WHO MODEL PRESCRIBING INFORMATION

DRUGS USED IN SEXUALLY TRANSMITTED DISEASES AND HIV INFECTION

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Drugs used in Sexually Transmitted Diseases and HIV Infection

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Geneva

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Preface

WHO's revised drug strategy, as adopted in resolution WHA39.27 of the Thirty-ninth World Health Assembly in 1986, calls for the preparation of model prescribing information, which is being developed to complement WHO's Model List of Essential Drugs.[1] The objective is to provide source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, drug compendia and similar material.[2]

The information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug that is appropriate to circumstances prevailing in each of WHO's Member States and that some countries have already formally adopted texts of their own that have a statutory connotation.

This volume has been reviewed by internationally accredited experts, by all members of WHO's Expert Advisory Panel on Drug Evaluation and by members of WHO's Expert Advisory Panel on Venereal Diseases, Treponematoses and Neisseria Infections. It has also been reviewed by certain nongovernmental organizations in official relations with WHO, including the International Federation of Pharmaceutical Manufacturers Associations, the International Pharmaceutical Federation, the International Union of Pharmacology and the World Federation of Proprietary Medicine Manufacturers.

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[1] *The use of essential drugs. Sixth report of the WHO Expert Committee.* 1995 (WHO Technical Report Series, No 850).

[2] For details of the three volumes of *WHO model prescribing information* already published, please see list inside back cover.

Drug dosage

Most drug doses are given per kilogram of body weight or as fixed doses calculated for adults of 60 kg.

Storage conditions

Readers are referred to *The international pharmacopoeia*, 3rd edition, vol. 4 (Geneva, World Health Organization, 1994) for definitions concerning containers for drugs.

Introduction

The dramatic rise in the incidence of sexually transmitted diseases that has been occurring globally for several decades has not yet been decisively stemmed. In some countries, reports indicate that changes in sexual behaviour have stabilized or even reduced the level of certain of these diseases, and intensive educational campaigns are currently directed to the prevention of human immunodeficiency virus (HIV) infection. None the less, several hundred million new cases of sexually transmitted diseases are still treated each year, with serious economic and social consequences as well as health implications. Directly or indirectly, this burden of disease is responsible for much sterility, stillbirth, miscarriage, blindness, brain damage, disfigurement, cancer and even death.

Patterns of infection and resistance

For reasons that remain uncertain, widespread changes in patterns of infection are occurring. In many countries chlamydial infections, genital herpes and warts are now more common than gonorrhoea and syphilis. Moreover, several infections no longer respond reliably to the more readily available antimicrobials. Strains of *Neisseria gonorrhoeae* with chromosomal or plasmid-mediated resistance to penicillin—and latterly to tetracycline—are now widespread. Multiresistant strains of *Haemophilus ducreyi* are emerging and resistance to metronidazole has been reported in *Trichomonas vaginalis*. Effective treatment for these diseases depends increasingly upon expensive third-generation cefalosporins and fluoroquinolones, which remain beyond the resources of many countries. There is a pressing case, given the rate at which drug resistance can emerge and spread, to maintain effective surveillance of resistance patterns within a global network of national and regional reference laboratories.

Other causative agents remain sensitive to most antimicrobial drugs, but the treatment of all sexually transmitted diseases becomes more complicated in patients who are infected with HIV or who are otherwise immunocompromised.

Management and control of sexually transmitted diseases

Control of sexually transmitted diseases requires:

- correct diagnosis
- effective early treatment
- education on avoidance of contact and prevention of transmission
- promotion and provision of condoms
- tracing, treating and counselling of sexual partners
- appropriate clinical follow-up.

If disease transmission is to be reduced, it is important that appropriate treatment is started when patients are first seen and that those at risk are persuaded to modify their sexual behaviour.

Where facilities allow, all patients with suspected sexually transmitted disease should be evaluated for HIV, syphilis, gonorrhoea and chlamydial infection. When it is feasible and resources permit, laboratory facilities should be made available for confirmatory testing and screening. As a minimum, laboratories should be equipped for light microscopy on wet mounts and Gram-stained slides. Dark-field microscopy for *Treponema pallidum* is difficult, and requires an excellent microscope and highly trained technicians.

It is inevitable that, at primary care level, sexually transmitted diseases will generally be treated solely on the basis of clinical presentation as genital ulcer disease, urethral discharge in men or vaginal discharge in women. A single-dose oral regimen should be used whenever this is an effective option. When repeated oral doses are prescribed for ambulatory patients, and in particular when sustained effective plasma concentrations of an antimicrobial are crucial to success, drug administration should be supervised whenever practicable.

A number of flow-charts are presented in the annex (pages 82–90) to assist in the empirical management of the most commonly encountered syndromes and in the selection of appropriate treatment in primary health care facilities. Their purpose is to help clinicians to manage patients on the basis of

the epidemiological, clinical and therapeutic information available. The charts are designed to provide a framework for evaluation and treatment, but should not replace clinical judgement and need to be adapted to local circumstances. Particular attention must be paid to the prevalence of antibiotic resistance among causative organisms whenever data are available.

In the following sections on individual diseases, emphasis is placed upon the importance of microbiological confirmation of both the diagnosis and the antibiotic sensitivity of the causative pathogen, even though this is still unattainable in many clinical settings.

Gonorrhoea

Gonorrhoea, which results from infection with the Gram-negative bacterium *Neisseria gonorrhoeae*, poses a considerable public health problem. Strains resistant to penicillin, tetracycline and doxycycline are widespread. This has created a demand for expensive antibiotic therapy, which cannot be met in less developed countries.

Primary infection through sexual contact can involve the mucosal surfaces of the urethra, the cervix, the rectum or the oropharynx. Gonococcal conjunctivitis and vulvovaginitis can occur in newborn infants as a result of infection during delivery when the mother has endocervicitis.

The inflammatory response to urogenital infection is varied. In men, signs of rapidly progressive purulent urethritis typically occur within a few days; patients may occasionally present with acute onset of a painful swollen scrotum. When treatment is inadequate or delayed, acute prostatitis, periurethral abscess and urethral stricture may develop. In women, early endocervical infection sometimes causes mild vaginal discharge. Untreated, it often progresses to pelvic inflammatory disease, which can cause acute or chronic abdominal pain, menstrual disturbance, infertility or ectopic pregnancy.

Gonococcal conjunctivitis is a medical emergency. Whereas the inflammatory response can be mild in adults, it is always severe in infants and progresses rapidly to corneal ulceration, perforation and blindness.

Haematogenous dissemination can occur if gonorrhoeal infections are not effectively treated at an early stage. Metastatic complications are varied. Serious lesions, which are rare, include meningitis, endocarditis and acute destructive monoarthritis with synovial effusion.

Confirming the diagnosis

In men, urethral discharge is the most common presenting symptom of sexually transmitted disease. Gonococcal and chlamydial infections often coexist. Less commonly, *Trichomonas vaginalis* is implicated in single or mixed infections. Focal intraurethral lesions, including genital herpes, warts and syphilitic chancre, are also sometimes responsible.

In women, gonorrhoea causes cervicitis, which may result in vaginal discharge. Examination should be undertaken to exclude a localized lesion, and endocervical and vaginal specimens examined microbiologically whenever possible to establish or exclude candidosis, trichomoniasis or "bacterial vaginosis", a condition ascribed to replacement of the lactobacilli of the vagina by *Gardnerella vaginalis* and vaginal anaerobes.

Gonorrhoea can be confirmed in men in over 90% of cases by demonstrating Gram-negative intracellular diplococci in urethral smears. Examination of cervical smears is considerably less reliable in most populations of patients. Cultures should be prepared when microscopy results are negative. *Chlamydia trachomatis* cannot be demonstrated by direct light microscopy and few clinics have the facilities either to culture the organism or to perform antigen-detection tests based on immunofluorescence or enzyme-linked immunosorbent assay (ELISA).

Ideally, blood samples should be taken for serological tests to exclude concurrent syphilis.

Treatment

Since *Chlamydia trachomatis*—which is now the most prevalent cause of sexually transmitted urethritis in developed countries—frequently coexists with gonococcal infection, all patients with gonorrhoea should also be treated concurrently for chlamydial infection unless microbiological facilities exist to exclude it. Sexual partners should be treated simultaneously. Ideally, all pregnant women should be screened clinically and, if necessary, by culture for gonorrhoea during their first antenatal visit and again, if they are considered to be at high risk, during the third trimester.

Antimicrobial therapy can be selected with confidence only when information is maintained on both the *in vitro* susceptibility of locally prevalent strains of gonococci and the clinical efficacy of treatment. Drug resistance can be either chromosomal or plasmid-mediated.

Chromosomal resistance rapidly rendered sulfonamides obsolete as antigonococcal drugs. Strains have latterly emerged that are highly resistant—either singly or multiply—to penicillins, tetracyclines, spectinomycin, erythromycin, thiamphenicol and cefalosporins. Cross-resistance between penicillin and second- and third-generation cefalosporins has seriously compromised the value of cefoxitin and cefuroxime in the treatment of gonorrhoea in many areas. Reduced *in vitro* susceptibility of some strains to cefotaxime, ceftriaxone and newer quinolones has been recently reported, but the clinical efficacy of these drugs is not yet impaired.

Plasmid-mediated resistance has been recognized more recently and it spreads more rapidly. It has long compromised the value of penicillins and, more recently, of tetracyclines as antigonococcal drugs. Several different penicillinase plasmids have now been identified that encode the same TEM-1 β-lactamase, and at least one of these also confers some resistance against non-β-lactam antibiotics. In some areas strains carrying one of these plasmids have also been found to carry chromosomal resistance. Strains exhibiting high levels of plasmid-mediated resistance to tetracycline were first identified in North America in 1985. They have since been found in northern Europe and Africa, but their overall prevalence remains uncertain.

WHO is establishing a network of regional coordinating surveillance centres to collate geographically specific information on the susceptibility of gonococci to reference antimicrobials and to promote the standardization of testing methods. The participation of laboratories in both developed and developing countries is encouraged.[1]

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[1] *Global surveillance network for gonococcal antimicrobial susceptibility.* Geneva, World Health Organization, 1990 (unpublished document WHO/VDT/90.452; available on request from Sexually Transmitted Diseases, World Health Organization, 1211 Geneva 27, Switzerland).

Uncomplicated genital and anal infections

Unless the infection is expected to be responsive to one of the less expensive antimicrobials, patients should receive a single intramuscular dose of either ceftriaxone, 250 mg, or spectinomycin, 2 g. A single oral dose of ciprofloxacin, 500 mg, or an equivalent fluoroquinolone is comparably effective, but should not be administered during pregnancy. Oral cefalosporins, such as cefixime 400 mg, are alternatives.

In some countries, locally acquired strains of gonococci are also susceptible to a single intramuscular dose of kanamycin, 2 g, or an oral course of thiamphenicol, 2.5 g daily for 2 days. The combination sulfamethoxazole (400 mg)/trimethoprim (80 mg), 10 tablets once daily for 3 days, is effective in areas where gonococci remain fully sensitive, but regular monitoring of the efficacy of this regimen is recommended.

Resistance to the penicillins is now so widespread that they are no longer of any practical value in the treatment of gonorrhoea.

Pharyngeal infection

Some of the regimens effective in genital gonorrhoea are unreliable in pharyngeal infections. Those most widely advocated are a single intramuscular injection of ceftriaxone, 250 mg, or sulfamethoxazole (400 mg)/trimethoprim (80 mg), 10 tablets once daily for 3 days.

Disseminated infection

Relatively high and extended parenteral dosage is necessary in disseminated infection. For gonococcal arthritis and most other foci of infection, a 7-day course of either ceftriaxone, 1 g given intramuscularly or intravenously once daily, or spectinomycin, 2 g given intramuscularly twice daily, is usually effective. Other third-generation cefalosporins, which may need to be given more frequently, are of value where neither of these drugs is available. When there is evidence of meningeal or endocardial involvement, treatment should be extended to 2 weeks or 4 weeks respectively.

Gonococcal conjunctivitis

This condition threatens sight and progresses rapidly. Since it is highly contagious, every effort should be made to prevent

transmission of infection. Effective barrier nursing and scrupulous hand-washing by all attendants are essential. Adult patients should be admitted to hospital where this is feasible until the infection has resolved. Antimicrobial therapy should be started immediately and the eyes should be frequently irrigated with saline. A single intramuscular dose of ceftriaxone, 250 mg, or spectinomycin, 2 g, or an oral dose of ciprofloxacin, 500 mg, is usually effective. When these are not available a single intramuscular dose of kanamycin, 2 g, may be substituted.

Infants with diagnosed ophthalmia neonatorum and all those born to mothers with proven or presumptive gonococcal infection should immediately receive a single intramuscular dose of ceftriaxone, 50 mg/kg (to a maximum of 125 mg). If this is not available, spectinomycin, 25 mg/kg (to a maximum of 75 mg), or kanamycin, 25 mg/kg (to a maximum of 75 mg), may be substituted. When systemic treatment is not available, tetracycline ointment, 1%, should be instilled into each eye hourly pending referral of the infant if infection is confirmed.

Prevention of ophthalmia neonatorum

All infants should receive topical antigonococcal therapy immediately after birth. Tetracycline ointment, 1%, should be applied after gently cleaning the eyelids. Erythromycin ointment, 1%, is as effective, but more expensive. Silver nitrate eye drops, 1%, are similarly effective, but more toxic.

Chlamydial infections

Lymphogranuloma venereum

Lymphogranuloma venereum, which is highly prevalent in many tropical countries, was first associated with *Chlamydia*, a genus of obligate intracellular parasites, in the 1930s. The serotypes of *Chlamydia trachomatis* involved, L_1, L_2 and L_3, are distinct from those associated with other sexually transmitted chlamydial infections.

The primary genital lesion is rarely demonstrable in women, but usually occurs in men as a painless ulcer on the penis that heals within a few days. After a latent period of days or months, an acute, fluctuant inguinal lymphadenopathy develops. Left untreated, the inflammatory masses, or buboes, extend into neighbouring tissues and often ulcerate to form chronic sinuses and fistulae. In the late stage of the disease, chronic lymphatic obstruction results in lymphoedema of the genitalia. The disease is seen in its acute phases more frequently in men but the late sequelae are often more severe in women.

Treatment

In the acute stage, the disease usually responds to appropriate oral antimicrobial therapy, although treatment may need to be extended for more than 14 days. Tetracycline, 500 mg four times daily, or doxycycline, 100 mg twice daily, is effective. When tetracyclines are inappropriate, as during pregnancy (since they are potentially toxic for both fetus and mother) and in children under 8 years of age, they may be replaced either by erythromycin, 500 mg four times daily, or by a sulfonamide such as sulfadiazine, 1 g four times daily.

Fluctuant lymph nodes should be aspirated through healthy skin. Incision and drainage or excision of acutely inflamed nodes is contraindicated since it delays healing, but strictures, fistulae and other late sequelae may require surgical intervention.

Other chlamydial infections

Over the past 30 years, other serotypes of chlamydiae (D–K) have become highly prevalent everywhere, and are now the most common sexually transmitted pathogens in industrialized countries. They are implicated in over half of all cases of non-gonococcal urethritis in men. Infection may cause epididymitis and, in homosexual men, chronic proctitis. In women, infection tends to be asymptomatic or non-specific, and is associated more often with cervicitis, salpingitis and endometritis than with dysuria and pyuria. Reiter syndrome, which is characterized by conjunctivitis, arthritis and urethritis, has also been associated with chlamydial infection, besides occurring as a sequel to dysenteric illness.

Infection during pregnancy is associated with premature delivery, low birth weight, neonatal death and postpartum endometritis. More than half the surviving infants born to women with cervical infection develop purulent conjunctivitis (chlamydial ophthalmia); others develop pneumonia; rarely the vagina, pharynx or rectum is also infected.

Urethritis, which is confirmed by identifying polymorphonuclear leukocytes in the discharge, is most commonly caused by *Neisseria gonorrhoeae, Chlamydia trachomatis* and human (alpha) herpesviruses (herpes simplex viruses). However, in one-third of cases seen in centres with fully equipped microbiological facilities no pathogen can be detected. Unless gonorrhoea can be excluded with confidence by microscopy and culture, patients with presumed chlamydial infections and their recent sexual partners should also be treated concurrently for gonorrhoea.

Treatment

Chlamydial infections involving the urethra, the endocervix, the eye and the rectum usually respond to a 7-day oral course of tetracycline, 500 mg four times daily, or doxycycline, 100 mg twice daily. During pregnancy and in other situations in which tetracyclines are contraindicated, erythromycin, 500 mg four times daily for 7 days, or—in the event of intolerance—a sulfonamide should be substituted. In every instance, sexual partners should be treated simultaneously.

Antimicrobial resistance to recommended regimens has not been reported, but patients should be advised to return for consultation if symptoms persist. Recurrence may result from non-compliance or failure to treat sexual partners. When symptoms persist or recur after apparently adequate treatment, both patient and partner(s) should be referred for laboratory investigation.

In some developed countries where there is a high prevalence of chlamydial infection, all pregnant women are now screened by means of direct immunofluorescence or ELISA antigen-detection tests and rapid-culture techniques during the first antenatal visit, and again—if they are considered to be at high risk—during the third trimester.

As recommended on page 10, all babies with ophthalmia neonatorum should be treated immediately for gonorrhoea. Only if they fail to respond should they be treated for chlamydial infection; erythromycin syrup, 50 mg/kg administered daily in four divided doses for 2 weeks, is usually effective. This course may be repeated should inclusion conjunctivitis recur on withdrawal of treatment. Infantile chlamydial pneumonia requires extended antimicrobial therapy.

Vaginitis

Vaginal discharge that occurs only premenstrually or at the time of ovulation or that is associated with the use of an oral contraceptive or an intrauterine device is likely to be physiological. Non-physiological discharge not associated with gonococci, chlamydiae, *Trichomonas vaginalis* or *Candida albicans* usually results from bacterial vaginosis, which is ascribed to replacement of the lactobacilli of the vagina by *Gardnerella vaginalis* and vaginal anaerobes. Discharge can also be associated with focal infective lesions including syphilitic chancre, herpes and warts, and with non-infective conditions including cervical ectropion, polyps and neoplasms.

In most primary health care settings, vaginitis has to be treated symptomatically. Whenever possible, however, and particularly in high-risk patients, the diagnosis should be confirmed microbiologically. *Candida albicans* can usually be identified as Gram-positive spores and mycelia in smears taken from the vaginal wall. *Trichomonas vaginalis* is readily seen microscopically in a wet preparation of an isolate from the posterior fornix, provided that light is reduced by closing down the shutter. *Neisseria gonorrhoeae* can sometimes be demonstrated as Gram-negative intracellular diplococci in isolates taken from the mucous membranes of the endocervix and the urethra but, because many infections are missed on microscopy, cultures should also be prepared when microscopy results are negative. Facilities for isolating *Chlamydia trachomatis* are available only in the most well equipped laboratories. Bacterial vaginosis can often be diagnosed by a reduction in the numbers of lactobacilli and by the presence of "clue cells" (cornified squamous epithelial cells, heavily coated with bacteria). The vaginal discharge has a characteristic fish-like odour that is heightened by adding 5–10% potassium hydroxide to a few drops on a glass slide.

Candidosis

Most infections are cured by nystatin pessaries, 100 000 International Units (IU). Two inserted nightly for 2 weeks are

usually effective, but in some areas nightly doses as high as 1000000IU are required. More rapid cures can be obtained with a more expensive imidazole preparation such as clotrimazole or miconazole, 200mg applied intravaginally daily for 3 days. Vulval irritation may be relieved by local nystatin or clotrimazole cream. A relapse shortly after initial therapy should be treated with a longer course of imidazole therapy, for example clotrimazole, 100mg daily for 12 days. Both acute and recurrent infections can now be cured most rapidly and reliably with a single oral dose of fluconazole 150mg or with two doses of itraconazole, 200mg, taken on the same day, but these treatments are expensive.

The risk of reinfection can be reduced by use of barrier contraceptives, antifungal creams and attention to hygiene. Should candidosis recur, sexual partners should also be treated since men may be infected asymptomatically, and other possible predisposing factors, including use of an oral contraceptive and tight or insulating clothing, should be discussed with the patient.

Trichomoniasis

Metronidazole, 2g as a single oral dose, cures the large majority of infections. Cure rates of up to 90% have been reported when sexual partners, who are usually asymptomatic, are treated simultaneously. Coincident bacterial vaginosis attenuates the effectiveness of the treatment. Patients who do not respond satisfactorily to single doses should receive metronidazole, 400–500mg orally twice daily for 7 days, which should also clear bacterial vaginosis.

Because metronidazole has been shown to be teratogenic in animals at massive dosage, trichomoniasis is best managed by local therapy during pregnancy and lactation. Pessaries of clotrimazole will at least attenuate the symptoms.

Infections in neonates usually resolve spontaneously within a few weeks. If signs are still evident 4 weeks after birth, the infant should receive metronidazole, 5mg/kg orally three times daily for 5 days.

Bacterial vaginosis

Oral metronidazole, 400–500 mg twice daily for 7 days, is highly effective. Male partners are not routinely treated but, since the disease is associated with high-risk sexual behaviour, it is advisable to evaluate male partners for evidence of other infections.

Pelvic inflammatory disease

Acute pelvic inflammatory disease, primarily involving the endometrium and fallopian tubes, is often a consequence of sexually transmitted disease. The pathological agents most commonly involved are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. However, bacteria present in the normal vaginal flora, including streptococci, *Escherichia coli*, *Haemophilus influenzae* and anaerobes such as *Bacteroides*, *Peptostreptococcus* and *Peptococcus* spp., also often contribute. Trauma to the endocervical canal from an intrauterine device may facilitate the ascent of these organisms into the endometrial cavity.

The condition frequently causes pain, dyspareunia, vaginal discharge, dysuria and fever, and sometimes nausea and vomiting. Pelvic tenderness is often prominent on bimanual examination of the cervix. Untreated, the chronic inflammatory reaction may have long-term sequelae, including persistent abdominal discomfort, sterility, tubal pregnancy and menstrual disturbances. The diagnosis should be considered in all sexually active women complaining of lower abdominal pain and—because it can also be asymptomatic—in all women with sexually transmitted disease.

Ideally, all patients in whom the diagnosis is established should be admitted to hospital. Where this is not feasible, priority should be given to adolescents, pregnant women, patients with a suspected pelvic abscess, those who have signs suggestive of appendicitis or ectopic pregnancy and patients with severe symptoms that do not respond to outpatient treatment.

Treatment

If an intrauterine device is in place, it should be removed.

Since mixed infections are common and precise microbiological diagnosis is rarely feasible, a treatment regimen should be chosen that is active against all the common causal organisms. The objective is to relieve symptoms and, in particular, to arrest progressive tubal damage.

Ambulatory patients have been successfully treated with a single-dose therapy for uncomplicated gonorrhoea, such as intramuscular ceftriaxone, 250 mg, followed by a 10-day oral course of doxycycline, 100 mg twice daily, or tetracycline, 500 mg four times daily, for chlamydial infection taken concurrently with metronidazole, 500 mg three times daily, for anaerobic infections.

Regimens for hospitalized patients based on (a) ceftriaxone, 250 mg injected intramuscularly twice daily, with doxycycline, 100 mg given orally or intravenously twice daily, or (b) twice-daily oral doses of ciprofloxacin 500 mg, doxycycline 100 mg and metronidazole 400–500 mg should be continued for 4 days or for 48 hours after clinical improvement and then followed by doxycycline, 100 mg given orally twice daily for 10–14 days. Other regimens based on penicillins in combination with β-lactamase inhibitors, quinolones, monobactams and carbapenems are still being evaluated.

Severely ill patients should receive intravenous doses of gentamicin, 1.5 mg/kg , and clindamycin, 900 mg, three times daily for a minimum of 4 days and for at least 48 hours after clinical improvement, followed by oral doxycycline or tetracycline for 10 days.

Syphilis

After many years of decline in the northern hemisphere, resulting from the success of penicillin therapy, syphilis, which is caused by the spirochaete *Treponema pallidum*, is again increasing in incidence in North America. In less developed countries, where the disease has remained relatively common, the primary illness frequently remains untreated and the late sequelae are still encountered.

Transmission results almost exclusively from sexual contact with infected persons, but infection can also be transmitted from mother to fetus during pregnancy and through blood transfusion. The primary genital ulcers (or chancres)—which are typically solitary, "punched out", indurated, painless lesions with a clear exudate—appear 9–90 days after exposure and heal spontaneously within a few weeks. Although the chancre is morphologically distinctive, it should ideally be differentiated microbiologically from other causes of ulceration, including genital herpes, chancroid and Behçet disease.

Untreated, and within a period of 2–6 months, the disease enters the secondary phase, which is characterized by a transient, variable skin rash and generalized low-grade lymphadenopathy, accompanied occasionally by focal involvement of the eye, meninges, parotid glands or viscera. Similar episodes, which seldom persist for more than a few weeks, may recur within the first 3 years. Infectivity subsides after this time, although congenital transmission has been reported even up to 10 years after initial infection.

Infection of the central nervous system can occur at any time in the course of the disease and should always be considered in differential diagnosis when a patient with untreated syphilis of more than 2 years' duration presents with a neurological abnormality. From 5 to 50 years may elapse after the disease becomes quiescent before the tertiary manifestations—benign late syphilis and cardiovascular syphilis—become evident.

Fetal infection may occur at any time throughout pregnancy, and infectivity approaches 100% when the mother has untreated primary or secondary disease. Clinical evidence of infection is often not present at birth and it may be missed until the lesions of late congenital syphilis begin to appear during childhood. In the more affluent countries, preventive measures, including widespread screening, treatment and contact-tracing, have been highly successful, with the result that congenital syphilis has been virtually eliminated where pregnant women are routinely screened for the disease.

Confirming the diagnosis

Clinical suspicion of syphilis can be difficult to confirm. During the primary and secondary phases of the disease, repeated searches should be made by dark-field microscopy for spirochaetes in exudates from lesions. Serological tests do not become positive for at least 2 weeks after the appearance of the primary lesion. Two of these tests are specific for treponemal diseases: the fluorescent treponemal antibody absorption (FTA-Abs) test and the *Treponema pallidum* haemagglutination test. The first usually becomes positive during the third week of the primary stage, while the second often takes longer to give positive results. Subsequently, both tests often remain positive for life even when prompt, effective treatment is given. For this reason, quantitative but less specific tests, the Venereal Disease Research Laboratory (VDRL) test and the rapid plasma reagin (RPR) test, are more useful for screening and prognostic purposes. These are flocculation tests that depend upon the presence of a less specific antibody (reagin) in the serum.

All pregnant women should be screened for syphilis by means of a non-specific test during their first antenatal visit and again, if they are considered to be at high risk, in the third trimester. Those who are positive on serological testing should receive antisyphilitic treatment unless it is certain that they have been treated adequately in the past. Retreatment is then unnecessary unless the titre in the VDRL or RPR test rises fourfold or more on sequential testing, or recent sexual contacts are known to have infectious syphilis.

The risk of congenital syphilis is remote if the mother has been treated with penicillin during pregnancy. Nevertheless, all infants born to seropositive mothers should be examined at birth and at monthly intervals for 3 months, since passive transfer of antibodies from a previously infected mother can invalidate serological diagnosis of active disease in the child for as long as 12 weeks. Infection can be confirmed by detection of IgM antibodies specific to *Treponema pallidum* in the infant's serum, but the test can be undertaken only in highly specialized laboratories. The simple FTA-Abs test, which detects labelled antibodies to human IgM, is easier to perform but false-positive results are likely unless the isolated IgM fraction of the infant's serum is used.

All seropositive infants and all infants born to seropositive mothers who have not received adequate treatment during pregnancy should be treated promptly. Infants of mothers infected late in pregnancy may be both asymptomatic and seronegative at birth. They should be treated where clinical and serological monitoring at monthly intervals for at least 3 months cannot be reliably undertaken, when it is uncertain whether the mother has received adequate treatment with penicillin, or when antibiotics other than penicillin were used.

Abnormalities in the cerebrospinal fluid may develop in any patient with syphilis. Examination of a sample is vital in the investigation of suspected neurosyphilis. The disease should be confirmed or excluded in any patient who presents with cranial nerve lesions, or optic or auditory symptoms of uncertain cause. Negative serological tests virtually exclude neurosyphilis, but positive tests require careful interpretation. Because the serological abnormalities are persistent, they provide evidence of both previous and current infection.

Radiological assessment, as well as serological testing, is important in the diagnosis and subsequent management of cardiovascular syphilis.

Treatment

Where facilities and resources are available, all patients and their contacts should be additionally tested and treated, as

appropriate, for chlamydial infection, gonorrhoea and HIV infection according to national policy.

Early syphilis

In cases of not more than 2 years' duration, two alternative regimens are widely used: a single dose of benzathine benzylpenicillin, 2.4 million IU (given, because of the large volume, as two intramuscular injections at separate sites), or a 10-day intramuscular course of procaine benzylpenicillin, 1.2 million IU daily.

However, some authorities recommend that all patients with either secondary or latent syphilis should receive more prolonged treatment: either intramuscular benzathine benzylpenicillin, 2.4 million IU once weekly for 3 consecutive weeks, or intramuscular procaine benzylpenicillin, 1.2 million IU daily for 2 weeks.

Late syphilis (other than neurosyphilis)

Prolonged courses of penicillin should be administered to all patients with benign late syphilis, cardiovascular syphilis, and latent syphilis that is likely to be of more than 2 years' duration. Treatment may be given either as a 3-week intramuscular course of procaine benzylpenicillin, 1.2 million IU daily, or as three consecutive weekly intramuscular injections of benzathine benzylpenicillin, each of 2.4 million IU.

Neurosyphilis

Higher dosages are necessary in patients with neurosyphilis to ensure that the penicillin level in the cerebrospinal fluid does not fall below the minimum inhibitory concentration throughout the period of treatment. This requirement is most reliably met by administering benzylpenicillin, 4 million IU intravenously every 4 hours for 2 weeks. Alternatively, provided that compliance is ensured, single intramuscular injections of procaine benzylpenicillin, 1.2 million IU, can be given daily for 2 weeks in combination with oral probenecid, 500 mg four times daily.

Syphilis in pregnancy

Syphilis should be treated immediately at all stages of pregnancy as recommended in the above regimens. Treated patients should remain under close supervision throughout

pregnancy to ensure that any reinfection is promptly diagnosed and treated.

Congenital syphilis

In children aged up to 2 years, congenital syphilis usually responds well to adequate doses of penicillin, although recovery may be slow in seriously ill patients with extensive involvement of the skin, mucous membranes, bone and viscera. Pneumonia and other intercurrent infections can rapidly supervene, particularly when there are signs of malnutrition.

When the cerebrospinal fluid is abnormal, the infant should receive either a 10-day course of benzylpenicillin, 50 000 IU/kg daily given intravenously or intramuscularly in two divided doses, or procaine benzylpenicillin, 50 000 IU/kg daily for 10 days as a single intramuscular injection. When the cerebrospinal fluid is normal, opinion is divided as to whether a 10-day course is required, or whether a single intramuscular injection of benzathine benzylpenicillin, 50 000 IU/kg, can be relied upon.

In children older than 2 years, higher and sustained blood concentrations of penicillin are required. Benzylpenicillin should be given for 2 weeks by intravenous injection of 200 000–300 000 IU/kg daily in divided doses, rising on a weight-adjusted basis to a maximum of 2.4 million IU daily.

Patients allergic to penicillin

Non-pregnant adult patients with early syphilis who are allergic to penicillin should receive a 15-day oral course of either tetracycline, 500 mg four times daily, or doxycycline, 100 mg twice daily. For patients with late syphilis including neurosyphilis, this regimen should be given for at least 30 days; the dose of doxycycline should be doubled for neurosyphilis.

Pregnant patients with early syphilis and confirmed allergy to penicillin are seriously disadvantaged because they cannot be given tetracyclines. It is important to assess and, when appropriate, to confirm by skin-testing any unsupported report of allergy in such a patient. Any attempt at "desensitization" is dangerous in a primary care setting. Erythromycin, 500 mg administered orally four times daily for 15 days, although

inferior, should be given in these circumstances. The baby must be assessed and treated after birth and the mother should be retreated with tetracyclines after delivery. Various alternative treatments have been proposed, but formal proof of efficacy is lacking.

Children with congenital syphilis and confirmed allergy to penicillins should receive erythromycin 7.5–12.5 mg/kg four times daily for a period of 30 days. During the first month of life the risk of allergy to penicillin is negligible.

Post-treatment follow-up

Patients with early syphilis who have been treated with adequate doses of penicillins should be evaluated clinically and serologically after 3 months, 6 months and 12 months to assess the effect of treatment and to detect possible reinfection. Patients treated with other antibiotics should be evaluated more frequently. Non-specific tests may remain positive at low titres indefinitely, even after adequate treatment.

Patients with cardiovascular syphilis or neurosyphilis should remain under observation for at least 3 years. In addition to clinical and serological evaluations, examination of cerebrospinal fluid and assessment of radiological changes may also be necessary. Retreatment should be considered when:

- clinical signs or symptoms of active syphilis persist or recur;
- a high titre in a non-specific test, such as a VDRL test result of 1:8, persists for 1 year or, in a pregnant woman, for 3 months;
- a lower titre in a non-specific test increases fourfold or more on sequential testing.

The cerebrospinal fluid should be examined before retreatment, unless there are conclusive grounds for establishing a diagnosis of early syphilis due to reinfection. In all other circumstances patients should be assumed to have late syphilis and be treated accordingly.

Genital herpes

Genital herpes can be caused by the ubiquitous human (alpha) herpesvirus 1 (herpes simplex virus 1), but is more frequently attributable to human (alpha) herpesvirus 2. Its prevalence increased considerably among young adults throughout the 1980s, particularly in North America. The disease is painful, recurrent and without cure.

Primary infection is usually signalled within a week by an extremely painful vesicular eruption on the external genitalia or other foci of sexual contact that subsequently ulcerates and resolves with crusting. This lesion resolves spontaneously and completely within 3 weeks, but the virus remains latent within the involved sensory nerve ganglia. Recurrences, which are usually milder and shorter than the primary attack, are often preceded by local tingling and paraesthesiae. Typically, they occur three or four times each year and they are liable to recur indefinitely. The incidence of the disease and the frequency, severity and duration of the attacks are greater in patients who are immunodeficient.

The evidence for placental transmission of infection is inconclusive. If it occurs, it is likely to result in fetal death and spontaneous abortion. Neonatal infection can occur if the mother's infection is active at the time of delivery. The risk is greatest during the primary infection and it decreases during the later stages of the disease. The disease can remain focal in the infant's skin, eyes and oral cavity, but in its disseminated form it can be fatal within a few weeks or cause permanent brain damage in survivors. When the mother has active genital lesions, delivery by caesarean section should be considered. Genital cultures taken late in pregnancy are poor predictors of shedding during delivery.

Confirming the diagnosis

Definitive diagnosis is dependent upon culture and identification of the herpesvirus but, in practice, this is often not possible. Treatment is then determined solely on the basis of

medical history and clinical examination. Syphilis and other causes of genital ulceration should be excluded beforehand.

Treatment

Patients should be warned that they are infectious to their partners when the lesions are present and that they should abstain from sexual activity as soon as they become aware of prodromal symptoms.

Specific topical treatment has little palliative effect, but pain may be partially relieved by simple analgesics. Bathing the lesions with saline is soothing and may facilitate micturition when this is painful. Urinary retention resulting from uncontrollable pain can necessitate hospital admission.

Although no radical cure is possible, the antiviral agent aciclovir inhibits replication of the virus to an extent that markedly reduces viral shedding. Treatment is extremely costly, but systemic therapy, when started early, may inhibit the formation of new lesions and also significantly accelerate healing, particularly during the first attack.

Primary attacks are usually treated with an initial 7-day oral course of aciclovir, 200 mg five times daily. In subsequent attacks, 5-day courses of treatment may suffice. Severe attacks in immunocompromised patients, characterized by widespread mucocutaneous involvement, should be treated in hospital.

Continuous suppressive therapy with aciclovir, 200 mg three times daily, markedly decreases the rate of recurrence among patients experiencing more than six episodes yearly. At present, there is no indication that this regimen has cumulative toxic effects, but some cases of resistance have been reported. Secondary infections should be treated with an appropriate antibiotic. The combination sulfamethoxazole/trimethoprim has the advantage, in some situations, that it has no antitreponemal activity and consequently does not mask syphilis.

Infants born to women with active genital ulcers or positive herpesvirus cultures should be isolated and examined frequently for signs of infection.

Chancroid

Chancroid, which results from infection by *Haemophilus ducreyi*, is the most common cause of genital ulceration in developing countries and its incidence has been rising with increasing rates of HIV infection. It is seen most frequently in men, typically on the prepuce, on the frenum of the glans penis and in the coronal sulcus after a short incubation period of 1–8 days. Chancroid is characterized by extremely painful, soft, destructive lesions, with undermined ragged edges and enlarged inguinal lymph nodes. Clinically, and in the absence of laboratory confirmation, the disease is readily confused with syphilis and genital herpes.

Secondary fusospirochaetal infection of advanced untreated lesions can lead to destructive ulceration of the entire external genital region, with formation of stenotic lesions, sinuses and, in women, rectovaginal fistulae.

Treatment

Fluctuant lymph nodes may need to be aspirated through intact skin when the patient is first seen. Effective antimicrobial therapy usually results in rapid healing of the ulcerative lesion and resolution of lymph-node enlargement within 14 days, but a high degree of resistance to therapy has been reported in patients with HIV infection.

Erythromycin given orally at a dose of 500 mg three times daily for 7 days is the preferred treatment for chancroid. Alternative, single-dose regimens are ciprofloxacin, 500 mg given orally, ceftriaxone, 250 mg injected intramuscularly, or spectinomycin, 2 g injected intramuscularly. Longer treatment courses may be necessary in HIV-infected patients. Benzathine benzylpenicillin should always be administered at the same time when facilities for dark-field microscopy and serological diagnosis of syphilis are not available. Resistance of *Haemophilus ducreyi* to sulfonamides, tetracyclines and penicillins now

renders these compounds largely ineffective. None the less, in some countries the combination sulfamethoxazole (400 mg)/ trimethoprim (80 mg) two tablets twice daily for 7 days, is still used with success.

Granuloma inguinale

Granuloma inguinale (donovanosis) is a chronic granulomatous infection caused by the Gram-negative encapsulated bacterium *Calymmatobacterium granulomatis* (formerly referred to as *Donovania granulomatis*), which occurs almost exclusively in tropical and subtropical regions. The infection usually involves the genitalia and perineum and is believed to be sexually transmitted, but it is not highly contagious.

The primary lesion, which appears after an incubation period of 9–90 days, starts as a papule and slowly develops into a painless, indurated granulomatous ulcer. Lymph nodes become enlarged (pseudobuboes) only when secondary infection supervenes. Secondary fusospirochaetosis results in large, painful and foul-smelling destructive lesions. Untreated, the primary infection may involve the whole of the external genitalia, the inguinal region and the anus. Metastatic lesions occur rarely in the skin of the back and breasts, the liver, the spleen and bone. Healing then results in intense scarring and stenoses that require surgery. Cancerous change can occur in long-standing lesions.

Treatment

Most infections are cured by a 2-week course of sulfamethoxazole (400 mg)/trimethoprim (80 mg), two tablets twice daily. Intramuscular streptomycin, which is also effective, is no longer recommended because of its ototoxicity and the need to reserve it for the treatment of tuberculosis.

Unresponsive infections have been treated successfully with a variety of regimens. Those most widely used are oral tetracycline, 500 mg four times daily for 2 weeks, chloramphenicol, 500 mg given orally four times daily for 3 weeks, and gentamicin, 1 mg/kg injected intramuscularly three times daily for 3 weeks.

The treatment of pregnant patients poses difficulties because of the potential toxicity of these antibiotics. Erythromycin

alone has proved disappointing. Better results are claimed when it is given in combination with lincomycin (each at an oral dose of 500 mg four times daily for 2 weeks), but this is associated with a risk of pseudomembranous colitis.

Genital warts

Genital warts (condylomata acuminata) are caused by a papillomavirus that cannot be cultured. They are nearly always transmitted by sexual contact. They occur most commonly on the external genitalia, but the perineum, anus and rectum—and in women, the vagina, cervix and urethra—may also be involved. They are diagnosed solely from their clinical features and need to be distinguished, in particular, from condylomata of secondary syphilis and molluscum contagiosum.

Many patients have other sexually transmitted diseases. All patients should be examined for both gonorrhoea and non-gonococcal urethritis and women for vaginal chlamydial infection, candidosis, trichomoniasis and bacterial vaginosis. Serological tests for syphilis should be undertaken.

Women should also be examined by colposcopy for cervical warts, and should be encouraged to undergo annual cytological testing because of uncertainty regarding the risk of warts undergoing malignant change.

Treatment

Local caustic applications are most often used, but treatment failures are frequent. Podophyllum resin, 10–25% in compound tincture of benzoin, should be applied carefully and sparingly to external genital, perianal and vaginal warts at weekly intervals up to a maximum of four applications; normal tissue should be avoided. Resin applied to the vaginal mucosa should be allowed to dry before it comes into contact with normal epithelium. Where it is available, podophyllotoxin is a less toxic alternative that can be applied by the patient. Trichloroacetic acid may be applied directly to the wart, but it is less effective and the treated area should be powdered with talc or sodium bicarbonate to remove excess acid.

External applications of podophyllum and podophyllotoxin should be removed by washing after 1–4 hours. Podophyllum

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is readily absorbed, locally destructive and teratogenic. Nei ther podophyllotoxin nor podophyllum resin should be ap plied to large skin surfaces, nor should they be used durin pregnancy.

Surgical removal, electrocautery, cryosurgery and laser treat ment may be used when topical applications have failed or ar contraindicated.

Electrosurgical removal under urethroscopy is preferred fo urethral warts, which should be suspected when meatal wart are recurrent. Intraurethral instillation of 5% fluorouraci cream may be effective, but the technique remains to be full evaluated. Cervical warts and warts occurring inside the rec tum always require surgical removal.

HIV infection, AIDS and associated infections

Several million individuals throughout the world are currently believed to be infected with human immunodeficiency virus (HIV), the causative agent of the acquired immunodeficiency syndrome (AIDS), and it is estimated that more than 40 million people will have been infected by the end of the millenium. It is now generally conceded that to cure HIV infection is an unrealistic goal. The retrovirus integrates itself into the host cell's genome where it can remain latent for long periods of time, virtually undetectable and out of range of any therapeutic intervention. Progress has been made, however, in developing antiretroviral drugs that can interfere with HIV replication by inhibiting viral reverse transcriptase. They prevent the spread of the virus to uninfected cells, but do not suppress the replication of HIV that is already integrated into the host genome. The drugs zidovudine, didanosine and zalcitabine are now widely registered for routine use in developed countries, but high cost precludes their use in developing countries. However, even when the resources are available to monitor the clinical response to therapy and to treat supervening complications effectively, these drugs provide only modest benefit. Experience gained with zidovudine indicates that, although it prolongs life and may also improve its quality, the median survival time from the diagnosis of AIDS among treated patients is less than 3 years.

HIV infection

Pathogenesis

Although there is still uncertainty about the course of HIV infection, it can be compatible with prolonged survival, with or without medical intervention. The latent period may be as short as 2 years or—as current projections indicate—as long as 2 decades. It has been estimated that approximately 50% of patients infected with HIV go on to develop full-blown AIDS within 10 years. Virtually every organ system can then be affected, either as a result of opportunistic or other infections

that supervene as the immune system becomes progressivel impaired, or from less clearly understood cytopathic and ma lignant changes. In infants infected at birth the course of th disease is more rapid. One in four develops AIDS within th first year of life and 80% have signs of the disease within years.

HIV is a retrovirus that is transmitted through sexual contac inoculation of infected blood or blood products, use of con taminated needles and vertical transmission from mother t offspring. Once in the bloodstream, the virus enters severa types of cells including lymphocytes, macrophages, Langer hans cells, and cells within the central nervous system. Th prime targets, however, are a subset of helper/inducer T lymphocytes and their precursors, distinguished phenotyp cally by the CD4 epitope expressed on their surface. The CD epitope is a receptor with affinity for glycoprotein in the outer envelope of the viral coat, which allows the virus to penetrat the cell. Once in the cell, the virus releases RNA which i transcribed by one of its enzymes, reverse transcriptase, int DNA. This, in part, becomes integrated into the cell's genet material and, when activated, is transcribed back into vira RNA. New virus particles are assembled at the cell membran and are released from the cell by a budding process.

Not until the virus has used the chromosomal apparatus in th way to multiply does it induce lethal cytopathic changes in th host cell. Initially, the CD4+ count in the peripheral blood maintained within normal limits. Subsequently, the count de creases either progressively or erratically as the viral loa within the body increases. The factors that determine the ra of viral replication are unknown, but there is speculation tha mycoplasmas and other opportunistic organisms includin viruses such as cytomegalovirus may influence the proces When the CD4+ count falls below 200/mm^3—that is, less tha 50% of the normal lower limit—the incidence of serious op portunistic infections rises sharply, apparently as a result damage to the remaining CD4+ cells both by soluble protei antigens and by cell-mediated stimulation.

Clinical manifestations

Seroconversion is sometimes signalled by an acute febrile illness that is readily mistaken for acute viral mononucleosis. Malaise, headache, photophobia, sore throat, gastrointestinal disturbances, cutaneous eruptions, arthralgia and myalgia are characteristic complaints, accompanied in some cases by transient signs of meningitis, encephalitis or peripheral neuropathy.

Later, before clinical manifestations of AIDS supervene, diffuse lymph-node enlargement may occur, sometimes accompanied by thrombocytopenia. The histological picture of follicular lymphoid hyperplasia is distinctive since the paracortical CD4+ cells are depleted, whereas other forms of lymphocytes are activated. Later, as the immune system is overwhelmed, the follicles involute and the nodes become atrophic. During this phase some patients develop an illness that has become known as AIDS-related complex. Typically, they complain of fevers, night sweats, diarrhoea and muscle pains. They lose weight and non-specific skin rashes may be troublesome. White and red cell counts tend to fall and thrombocytopenic purpura can occur. Oral candidosis or zoster may supervene, but at this stage opportunistic infections are unlikely to be life-threatening.

Ultimately, AIDS is heralded either by serious opportunistic infections or—in particular in sexually active homosexual men—by malignant disease, including lymphomas and, more specifically, by a prolific and virtually pathognomonic form of Kaposi sarcoma. The syndrome, which was described before HIV had been identified, was used to denote patients immunodeficient from an unknown cause who presented with one of these conditions. The term AIDS remains indelible in the public mind but, for scientific purposes, it has been superseded by detailed staging classifications of HIV infection,[1,2] which

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[1] United States Centers for Disease Control. Classification system for human T-lymphocytic virus type III/lymphadenopathy-associated virus infections. *Morbidity and mortality weekly report*, 1986, **35**: 334–339.

[2] Redfield RR, Wright CD, Tramont EC. The Walter Reed Staging Classification for HTLV-III/LAV infection. *New England journal of medicine*, 1986, **314**: 131–132.

provide useful criteria for selecting or stratifying patients admitted to clinical trials.

It is believed that over 90% of patients who develop AIDS eventually die from supervening infection. They have increased susceptibility to systemic infections that are prevalent within the population at large as well as to opportunistic infections that develop only in immunodeficient individuals. The former, which are typified by tuberculosis, oral candidosis and herpesviral infection, tend to occur earlier in the course of the disease than more strictly opportunistic infections such as *Pneumocystis carinii* pneumonia, cryptococcal meningitis and those responsible for the more variable manifestations of systemic disease, including infection with *Cryptosporidium* species, the *Mycobacterium avium–intracellulare* complex, cytomegalovirus and *Toxoplasma gondii*. Until it becomes possible to reverse the underlying immunological defect, prevention and treatment of these associated infections provide the most effective means of prolonging and improving the quality of life of patients with HIV infection.

Prevention and treatment of HIV infection

Preventive measures

In many countries, primary prevention is the only method of controlling HIV infection and AIDS. Measures to prevent HIV transmission include:

- Health education to modify sexual behaviour and to raise public awareness of the risks of HIV infection and AIDS.
- Intensified detection and treatment of other sexually transmitted diseases, since these conditions can facilitate the transmission of HIV.
- Encouraging the adoption of protective measures, for example through the promotion and provision of condoms and information on their correct use.
- Improved antenatal care for HIV-infected pregnant women.
- Sterilization of needles and screening of donated blood.

Treatment of AIDS and AIDS-related complex

The consensus is now firm that antiviral treatment with zidovudine, in conjunction with specific treatment for opportunistic and other infections, usually retards the progression of the disease—often for a year or more—in symptomatic patients. This clinical effect is accompanied by a rapid decrease in the titre of virus in the blood.

Daily treatment with zidovudine, 500–600 mg taken orally in divided doses at 4-hour intervals throughout the day, has been shown to extend survival time for up to 2 years in patients who have advanced AIDS-related complex or who have survived at least one episode of pneumonia due to *Pneumocystis carinii*. Treated patients feel better, gain weight, have fewer opportunistic infections and, in some cases, show improvements in AIDS-related dementia and other neurological changes. Kaposi lesions, in contrast, are largely or completely resistant to treatment, particularly among patients with a history of opportunistic infection.

The response to zidovudine is time-limited; the end stage of the disease is characterized by reduced sensitivity to the drug and the return of a high titre of virus in the blood. The decline in the response to zidovudine sometimes results from cumulative toxic effects, expressed as bone-marrow suppression or myopathy. In other cases it reflects the patient's weakening immune control over HIV replication and an increased viral load. Most frequently, however, it results from mutations in the HIV genome that increase its virulence or induce resistance to zidovudine. For example, the appearance of syncytium-inducing virus, which accelerates the progression of the disease by facilitating cell-to-cell spread, is caused by genetically determined changes in the protein envelope. Continued exposure to zidovudine also selects for several independent mutations that produce amino-acid substitutions in viral reverse transcriptase.

Didanosine, a nucleoside analogue that has similar beneficial effects to zidovudine, is used in patients who are intolerant of or unresponsive to zidovudine. It may be introduced in advanced disease when the effect of zidovudine begins to wane

but, as yet, no optimal time has been established for a chang in therapy. Although didanosine, like zidovudine, acts by in hibiting reverse transcriptase, its adverse effects are distin tive. Pancreatitis commonly occurs, and is occasionally fata while peripheral neuropathy is the most frequent dos limiting effect.

Zalcitabine, another recently approved nucleoside analogue, used in combination with zidovudine to treat patients who a deteriorating clinically or immunologically and who have CD4+ count of $<300/mm^3$. Its therapeutic effects are simil to those of didanosine. Pancreatitis rarely occurs, but painf peripheral neuropathy is common. Rash and stomatitis a also frequent, but usually transient even when treatment continued. Some HIV isolates resistant to didanosine hav shown cross-resistance to zalcitabine.

Treatment of early HIV infection

Considerable attention has recently been focused on the pote tial of suppressive lower-dose therapy in HIV-positive p tients with few or no symptoms. Initial evidence obtaine within the United States seemed encouraging, suggesting th low-dose zidovudine could slow the rate of progression AIDS in addition to averting the risk of myopathy and redu ing the incidence of myelosuppression. However, no su benefit was evident in a more extended multicentre tri undertaken in Europe. If treatment of early HIV infection we to be of practical value, there would need to be not only ev dence of therapeutic benefit but also assurance that such trea ment would be well tolerated and would not favour t emergence of viral resistance. The available evidence sugges that routine use of zidovudine in symptom-free HIV-positi individuals is unwarranted.

Prophylactic use of zidovudine

Zidovudine administered immediately after exposure claimed to suppress retroviral infections in animals. In view this, the practice has developed in many health care instit tions to offer staff a prophylactic course of zidovudi immediately after they sustain a puncture wound from potentially contaminated needle. Victims of rape are al sometimes offered this option. However, cases of failed pr

phylaxis are already on record. Moreover, since the rate of seroconversion following needle injury has been estimated to be less than 0.5%, a definitive assessment of the degree of any protection provided will need to be based on a considerable body of experience. In the present uncertainty, prophylaxis should be offered only when the patient has been informed of the level of risk of infection, the rationale of administering zidovudine, and what is known about the short-term and long-term toxicity of the drug.

Use of zidovudine during pregnancy and in children

Firm data from two independent studies undertaken in the United States indicate that prenatal and perinatal zidovudine therapy considerably reduces the risk of vertical transmission of HIV infection. However, more information is needed about the effect of maternal risk factors, the optimum timing of treatment and the minimum dosages required. To be certain that zidovudine has prevented and not merely suppressed the infective process, it will be necessary to maintain the children of zidovudine-treated mothers under extended observation.

Studies of the use of zidovudine in children with HIV infection have shown a profile of clinical benefit and dose-related toxicity similar to that observed in adults. Zidovudine has been used prophylactically in neonates born to infected mothers, and to treat children infected as a result of vertical transmission, blood transfusion or administration of contaminated factor VIII or other blood products. As yet, the optimal dosage, route and frequency of administration have not been determined. The regimens used have been roughly proportional to those recommended for adults.

Potential developments in treatment

Clinical trials are under way to determine the optimal sequential or combination regimens based on zidovudine, didanosine, zalcitabine and the more recently developed nucleoside analogue stavudine. Other combination treatments include antiviral drugs given with therapies based on immunomodulators such as interleukin-2, and zidovudine administered with prophylactic agents directed against

high-risk opportunistic pathogens. Recombinant interferon alfa combined with zidovudine has also shown promise in early trials. Administration of granulocyte/macrophage colony-stimulating factor may ameliorate the resulting neutropenia.

There is considerable evidence that effective immunization would offer the best prospect of reducing transmission and slowing the progression of HIV infection. However, although there have been encouraging developments in vaccine research, with a recent shift towards trying to stimulate cell-mediated immunity, a suitable vaccine for preventing HIV infection is still not available.

General features of associated infections

As already mentioned, infectious diseases constitute the immediate cause of death in over 90% of patients with advanced HIV infection. Some are caused by common pathogens, but many are opportunistic, meaning that they are caused by normally avirulent microbes, many of which are members of the commensal flora. Knowledge of these is incomplete and new forms of opportunistic infection attributed to previously unrecognized and uncharacterized microbes are still being discovered.

The incidence and spectrum of these infections differ in important respects from those associated with other immunosuppressive disorders. Whereas all immunocompromised patients are vulnerable to toxoplasmic encephalitis, oral candidosis and pulmonary tuberculosis, many opportunistic diseases including *Pneumocystis carinii* pneumonia and systemic infections due to *Cryptococcus neoformans*, cytomegalovirus, the *Mycobacterium avium–intracellulare* complex and *Cryptosporidium* species have, thus far, occurred almost exclusively in HIV-infected persons. The pattern of infection also varies between developed and developing countries. In some African countries as many as 50% of patients with AIDS also have active tuberculosis. In contrast, pneumonia due to *Pneumocystis carinii* is less frequent in these countries, apparently because many patients die before their immune defences are severely attenuated.

Limited information from controlled clinical studies suggests that regular administration of zidovudine reduces the incidence of opportunistic infections in patients with AIDS. It may also accelerate the rate of response to specific therapy. However, this benefit is time-limited, since the effects begin to wane among patients who have received zidovudine for more than a year. Moreover, since both zidovudine and some of the antimicrobials used to treat opportunistic infections are myelosuppressive, the blood count must be monitored with particular care during combined therapy. Since withdrawal of zidovudine may accelerate the rate of HIV replication, reduction of dosage is often preferable to temporary discontinuation.

The following sections describe the typical clinical course of the more common infections associated with HIV infection. However, it should be borne in mind that atypical presentations are frequent, disseminated disease is common, and two or more infections often occur concurrently. Prescribing information is provided for the most frequently used drugs, with the exception of antituberculosis drugs, since the treatment of tuberculosis is described in detail elsewhere (see footnote, page 44). Drugs whose high cost makes it unlikely that they will be available in many countries are not included.

Respiratory disease

From an early stage, HIV-infected patients are particularly vulnerable to common pathogens of the respiratory tract, including influenza viruses, pneumococci, *Haemophilus influenzae* and *Legionella* species. As immunological function continues to deteriorate, they also become susceptible to tuberculosis, non-specific mycobacterial infections and systemic mycoses. Ultimately, as the underlying disease advances, pneumonia due to *Pneumocystis carinii* becomes the main cause of death.

Pneumonia due to *Pneumocystis carinii*

Pneumocystis carinii is a protozoan that normally exists in the lungs as a commensal. Before the AIDS pandemic, it was rarely implicated as a human pathogen. However, more than 80% of patients with AIDS experience at least one episode of *Pneumocystis carinii* pneumonia and it is the most frequent

initial manifestation of the syndrome. Rapid multiplication of the organisms in small cystic foci in the alveolar septal walls throughout the lungs rapidly induces an irreversible fibrotic reaction.

Despite greater awareness and technical progress leading to earlier diagnosis of the disease and the important advances made in treatment and prophylactic management, *Pneumocystis carinii* pneumonia still causes more deaths than any other opportunistic infection.

The first signs of the disease often develop insidiously and are easily missed. Patients known to be at risk should be urged to report increasing shortness of breath or cough promptly. Chest X-rays sometimes reveal extensive infiltration, nodules or cavities, but at first presentation they may be misleadingly normal. Whenever practicable, attempts should be made to identify the organism, which may be demonstrable in specially prepared sputum smears or in bronchoalveolar washings.

Treatment

Oral or intravenous sulfamethoxazole/trimethoprim or intravenous infusions of pentamidine isetionate are often effective when administered at an early stage. Signs of improvement may not be evident for 4–8 days and treatment needs to be maintained, whenever possible, for at least 3 weeks. Both pentamidine and sulfamethoxazole/trimethoprim are associated with a particularly high incidence of toxic effects in AIDS patients and sulfamethoxazole, like zidovudine, is myelosuppressive.

When no improvement is evident after 4–8 days, clinicians often resort to switching to the other drug or even administering both concurrently. Additional candidate drugs are currently under assessment. Limited, but promising experience has recently been gained with eflornithine, a trypanosomicide that inhibits ornithine metabolism, and trimetrexate, a lipid-soluble analogue of methotrexate, which is a potent inhibitor of dihydrofolate reductase in *Pneumocystis carinii*.

The first few days of antimicrobial treatment are critical since the decomposition of many dead parasites exacerbates the pre-

existing inflammatory process and aggravates hypoxia. However, the risk of death at this stage can be substantially reduced if a corticosteroid — oral prednisolone or, when necessary, intravenous methylprednisolone — is administered as soon as antimicrobial therapy is started, if the patient's arterial oxygen tension is less than 70 mmHg (9.33 kPa). Prednisolone given orally at a dose of 40 mg twice daily for 5 days, followed by 40 mg daily for 5 days, and then 20 mg daily for 10 days has not demonstrably increased the vulnerability of patients to other opportunistic infections, with the possible exception of candidosis and alphaherpesviral disease.

Prophylaxis

Ideally, every patient who has been successfully treated for pneumonia due to *Pneumocystis carinii*, or who has a CD4+ lymphocyte count of less than 200/mm^3, should receive continuous prophylaxis. Various estimates place the 3-month relapse rate among patients not receiving prophylaxis at 10–40%; about one in five such episodes is fatal.

Until recently, reliance was placed largely on sulfamethoxazole/trimethoprim and pyrimethamine/sulfadoxine, but these were poorly tolerated by many patients. Pentamidine is too toxic to be given intravenously for prophylaxis. However, much of its systemic toxicity can be avoided by use of an aerosol formulation now available that is inhaled into the lungs; monthly inhalations substantially reduce the risk of re-infection. Unfortunately, widespread use of pentamidine in aerosol form has been accompanied by a rise in extrapulmonary infection with *Pneumocystis carinii*. In addition, concern has recently been expressed that resistance to antimicrobial agents may be emerging in *Pneumocystis carinii* isolates or that they may be developing virulence factors that enable them to cause disease in the elderly and other new groups.

Pulmonary tuberculosis

There are indications of a resurgence of tuberculosis everywhere where AIDS is prevalent. Among patients with advanced HIV infection, the disease causes substantial mortality. The initial signs of the disease may become apparent at any

time during the evolution of HIV infection. About half th cases present with extrapulmonary disease and pulmonar lesions are often atypical. Unilateral or bilateral infiltrates i the lower lobes are more common than upper lobe lesions an cavities.

There is no evidence, as yet, of atypical patterns of antibiot resistance in *Mycobacterium tuberculosis* isolates from AIDS pa tients. Limited retrospective data generated in the Unite States suggest that rates of treatment failure and relaps following standard antituberculosis therapy are comparab to those prevailing in the population at large, although th incidence of adverse reactions may be substantially highe Among patients who comply with the prescribed regime conventional therapy[1] results in rapid sterilization of sputu and radiographic improvement, and rates of relapse are lo Treatment is usually started with isoniazid, rifampicin an pyrazinamide. To prevent relapse, many clinicians try to co tinue treatment indefinitely unless this is precluded by dru toxicity. Studies are in progress to assess the potential of var ous regimens in primary preventive chemotherapy.

Histoplasmosis and coccidioidomycosis

In regions where the organisms *Histoplasma capsulatum* (va *capsulatum* and *duboisii*) and *Coccidioides immitis* are endemi patients with HIV infection are at risk of developing dissem nated histoplasmosis and coccidioidomycosis. In otherwis healthy persons such infections are either subclinical or sel limiting within the lungs.

The initial symptoms are often non-specific, but pulmonar involvement characterized by cough, fever, malaise an weight loss—and confirmed by radiological evidence of pu monary interstitial infiltrates—can be prominent. Nause vomiting and diarrhoea are common. Haematogenous di semination ultimately results in terminal septic shock. Diag

[1] For further information on the conventional treatment of tuberculosis, see: *Treatment tuberculosis: guidelines for national programmes*. Geneva, World Health Organization, 199 *WHO model prescribing information: drugs used in mycobacterial diseases*. Geneva, Wor Health Organization, 1991; and Piot P et al. *AIDS in Africa: a manual for physicians*. Genev World Health Organization, 1992: 52–54.

nosis is dependent upon demonstration of the organism in bronchoalveolar washings, biopsy material or cultures from blood or bone marrow. In severely ill patients, however, initiation of treatment is warranted on the basis of clinical findings and a positive test for serum antibody.

Amphotericin B in a total dose of 2–3 g has so far provided the only prospect of clinical improvement. To reduce the risk of immediate relapse, treatment with ketoconazole or lower doses of amphotericin B needs to be maintained indefinitely.

Neurological disorders

As many as 20% of HIV-infected patients develop neurological complications. Some of these apparently result from a direct encephalitic effect of HIV, and others are due to neoplastic lesions, notably lymphomas. Most, however, result from opportunistic infections. Toxoplasmic encephalitis accounts for most focal lesions, while cytomegalovirus and alpha-herpesviruses (herpes simplex viruses) are relatively rarely implicated. Life-threatening meningitis is usually due to *Cryptococcus neoformans* and only very occasionally to coccidioidomycosis or tuberculoma.

Toxoplasmosis

Toxoplasma gondii, a protozoan parasite of mammals, is transmitted when oocysts excreted by household pets or present in undercooked meat are ingested. Invasive forms enter the bloodstream to reach the brain, heart and lungs, where they form cystic aggregates that remain latent but subject to reactivation throughout the life of the host. In many communities most people have been infected by early adulthood, but otherwise healthy persons do not develop clinically evident disease. In HIV-infected patients, however, toxoplasmosis holds serious implications:

- Primary infection may result in focal necrotizing encephalitis and occasionally retinochoroiditis and pneumonitis as a result of the unrestrained multiplication of tachyzoites.
- Reactivation of latent bradyzoites produces focal neurological signs in some 30% of patients with AIDS.

Hemiparesis, cognitive disorders, seizures and other sign suggestive of an intracerebral space-occupying lesion ten to develop subacutely over several weeks, and they ar sometimes accompanied by symptoms of a diffus encephalopathy. Fever and headache can be prominent, bu meningeal irritation is infrequent. Changes in the cer ebrospinal fluid are usually non-specific.

- Congenital transmission of *Toxoplasma gondii* can occur as consequence of either a latent infection or a new primar infection in the mother. In many instances the parasit induces spontaneous abortion or fetal death. Children bor with signs of infection are generally severely ill, often with potentially fatal syndrome characterized by hydrocephalu hepatosplenomegaly with jaundice, mental retardation an chorioretinitis. Congenital disease that becomes apparer only later in life is usually less severe, but ocular or neuro logical impairment is common.[1]

Prevention

The risk of transmission can be reduced if meat is adequatel cooked and if vegetables and fruit are washed carefully befo they are eaten.

Treatment

A histopathological diagnosis of toxoplasmic encephalit should be established whenever possible, since non-infectiv conditions including lymphoma, Kaposi sarcoma and mult focal leukoencephalopathy may also cause focal neurologic lesions. Serological tests are of limited value and culture organisms from biopsy material may take several week Often, treatment has to be started empirically, sometimes o the basis of tomograms showing multiple discrete lesio within the brain, typically arranged in ring formation.

HIV-infected patients suspected of having active tox plasmosis, including children and severely ill pregna women, should receive pyrimethamine in combination with sulfonamide (usually sulfadiazine). Both drugs penetrate in

[1] For a discussion of the treatment of congenital toxoplasmosis, see *WHO model prescribi information: drugs used in parasitic diseases*, 2nd ed. Geneva, World Health Organizatio 1995.

the cerebrospinal fluid in therapeutically active concentrations. Relatively high dosages need to be given, despite the patients' vulnerability to adverse effects and the inability of many of them to tolerate treatment for more than 6 weeks. Leukopenia, thrombocytopenia and rash are common. Calcium folinate, which counteracts the blockade of folate metabolism in mammalian cells without affecting antiprotozoal activity, should be administered every third day to reduce the risk of anaemia. Patients should also remain well hydrated since sulfadiazine is poorly soluble in the urine.

Pyrimethamine has been used alone in patients intolerant of sulfonamides at dosages several times those normally recommended, but such regimens are associated with a greater risk of bone-marrow suppression. Intravenous clindamycin has also been used in these circumstances. However, whereas it is effective in the treatment of retinochoroiditis, its value in toxoplasmic encephalitis remains uncertain.

Because of the severity of toxoplasmosis in HIV-infected patients and the high rate of recurrence, suppressive therapy with lower daily dosages of pyrimethamine and sulfadiazine should be continued indefinitely after successful primary treatment whenever this is feasible.

Cryptococcal meningitis

Cryptococcus neoformans, a yeast-like fungus widely present in soil and, in greater concentrations, in bird excreta, causes disseminated disease in about 5% of persons with advanced HIV infection. It readily spreads from the lungs to the meninges (causing cryptococcomas) and, less commonly, to the bone marrow, genitourinary tract and skin.

The onset of cryptococcal meningitis is generally insidious. Fever and headache are often the only presenting signs. Nausea, vomiting and neck stiffness may be absent and focal neurological signs are uncommon. Sometimes there are no signs directly referable to the nervous system. Typical extraneural manifestations include skin lesions, pneumonitis and pleural effusion and retinitis. Untreated, the disease runs

a slowly progressive and ultimately fatal course. Early diagn
sis is usually dependent upon demonstration of cryptococc
antigen in the serum or culture of cryptococci from the ce
ebrospinal fluid.

Treatment

All patients from whom cryptococci are isolated should b
treated, even if they have no signs of infection, because of th
high risk of meningitis and disseminated disease. Treatme
with amphotericin B infused intravenously at a daily dose
0.5–1.0 mg/kg plus oral flucytosine has, until recently, offere
the only prospect of cure. Administration must be maintaine
for at least 6 weeks and until cultures of cerebrospinal flu
have been negative for 4 weeks. At this dosage amphotericin
may induce chills, fever or renal dysfunction, but prematu
withdrawal of treatment is rarely necessary. However, failu
rates are high and relapses are frequent unless, after the initi
course of daily treatment, weekly infusions can be maintaine
indefinitely.

Preliminary results suggest that fluconazole, itraconazole ar
other orally active triazole antifungal agents may be compa
ably effective in both treatment and prophylaxis. The results
one recent study suggest that fluconazole is also better tole
ated than amphotericin B.

Ophthalmological complications

HIV itself may occasionally induce retinal haemorrhage ar
optic neuropathy. In other cases, Kaposi sarcoma may sprea
to involve the conjunctivae, eyelids and orbit. However, visio
is more frequently compromised by infections with cytomeg
lovirus and sometimes *Toxoplasma gondii* or *Pneumocyst
carinii*.

Cytomegalovirus infections

Asymptomatic cytomegalovirus infections, which are wid
spread in most communities, are transmitted congenitally, b
sexual contact or by blood transfusion. In HIV-infected p
tients cytomegalovirus is a cause of retinochoroiditis, enteri
and pneumonitis and is often present, together with *Mycoba*

terium avium–intracellulare and human (gamma) herpesvirus 4 (Epstein–Barr virus), in patients in a state of advanced cachexia.

Nearly all cases of retinochoroiditis in HIV-infected patients are caused by cytomegalovirus. The visual loss is progressive and irreversible. Flame-shaped intraretinal haemorrhages superimposed on white granular necrotic patches are seen in the fundi.

Parenteral antiviral therapy with ganciclovir usually arrests progression of retinochoroiditis and cytomegalovirus enteritis, but pulmonary infection is often less responsive. Therapy must be sustained if prompt relapse is to be averted but, because ganciclovir is myelosuppressive, this can be impracticable. Foscarnet has been used as an alternative in this situation.

Febrile illness

Unexplained fever occurs frequently in HIV-infected patients. Diagnosis should be directed primarily to identifying pathogens causing illness that can be effectively treated, notably *Pneumocystis carinii*, salmonellae, cytomegalovirus and *Mycobacterium tuberculosis*.

Mycobacterial infections

Any of the known pathogenic mycobacteria can cause febrile illness in HIV-infected patients. In North America *Mycobacterium avium–intracellulare* is most commonly implicated, while in Africa tuberculosis is more common.

Infection with *Mycobacterium avium–intracellulare*, which can be isolated from a large proportion of patients with advanced HIV infection, may contribute substantially to the weight loss, inanition, fever and diarrhoea that typify AIDS. Acid-fast bacilli may be present in large numbers without provoking a granulomatous reaction and focal lesions can occur in virtually any organ system.

Treatment[1]

Mycobacterium tuberculosis can usually be differentiated fro non-specific mycobacteria by skilled examination of sputu smears. However, identification of non-specific mycobacter in clinical isolates does not necessarily establish their clinic relevance. Other pathogens should be sought when the dia nosis remains in doubt. It is important, none the less, to sta treatment promptly and to revise it, if necessary, in the light subsequent microbiological evidence.

Mycobacterium avium–intracellulare is usually susceptible clofazimine, cycloserine and ethionamide. Clofazimine generally preferred to treat disseminated disease since it selectively concentrated in the bone marrow and the reticul endothelial system. It is often administered in combinatic with rifampicin. However, the effect of treatment on morbidi and survival time remains uncertain.

Diarrhoeal disease

Symptoms of colitis or small-bowel watery diarrhoea are cor mon among HIV-infected patients. When they are severe the constitute the most distressing manifestation of HIV infectio Small-bowel diarrhoea can result from extensive Kapo lesions and sometimes from the cytopathic effect of HI However, most cases result from bacterial, protozoan or he minthic colonization. Some of these organisms, includir *Cryptosporidium* species, cytomegalovirus, *Mycobacteriu avium–intracellulare*, and *Isospora belli*, cause diarrhoea almo exclusively in patients with HIV infection. Others, includir *Giardia intestinalis*, *Entamoeba histolytica* and *Helicobacte Shigella* and *Salmonella* species, commonly cause intestin disease in homosexual men. In immunosuppressed patien some of these organisms, in particular salmonellae, are liab to cause disseminated disease.

Whenever possible, the cause of the diarrhoea should be estab lished and specific treatment provided. Failing this, manage ment is symptomatic. A high energy and protein intak reduces the degree of muscle wasting. Megestrol (a syntheti

[1] For the treatment of pulmonary tuberculosis, see page 43.

progestogen) is sometimes used to stimulate appetite. The use of antidiarrhoeal agents such as codeine phosphate is justified when symptomatic relief is the major consideration. The antimotility drugs diphenoxylate and loperamide should not be used in ulcerative inflammatory bowel disease or in the management of acute diarrhoea in young children because of the danger of toxic dilatation of the colon.

Cryptosporidiosis

Cryptosporidium species, long recognized as pathogenic protozoans in veterinary practice, have recently been identified as an important cause of persistent debilitating watery diarrhoea and weight loss in HIV-infected patients. Transmission, which occurs by the faecal–oral route, is particularly common among homosexual men and where sanitation is inadequate. The small bowel is extensively colonized and invasion of the biliary tree occasionally results in stenosis and cholecystitis. The organisms can be demonstrated in the stools only in iodine-stained wet mounts and by acid-fast staining of smears.

Spiramycin is of some value, but the outcome is uncertain and gastrointestinal irritation can be severe. Doses of 1–3 g daily have resulted in remission, but treatment may need to be extended for 4 months or more before the organisms are cleared from the stools.

Isospora belli infection

The frequency with which the protozoan *Isospora belli* causes diarrhoea in HIV-infected patients varies in different countries. It can be demonstrated in the stools by the techniques developed for *Cryptosporidium* species. Most cases are readily treated with sulfamethoxazole/trimethoprim.

Cytomegalovirus infection

Cytomegalovirus is an uncommon but potentially lethal cause of diarrhoea in HIV-infected patients. Any portion of the intestine may be involved and intense inflammation may result in perforation or substantial haemorrhage. Diagnosis is confirmed by endoscopy and demonstration of inclusion bodies in a biopsy specimen. Cytomegalovirus enteritis can usually be

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arrested with parenteral ganciclovir, but therapy must be sus tained if relapse is to be prevented.

Mucocutaneous and cutaneous eruptions

Most patients with HIV infection develop dermatological con ditions at some point in the course of the disease. A pathognomonic, highly proliferative form of Kaposi sarcoma is often the first clinical manifestation of AIDS. Among the infectious diseases, candidosis and, to a lesser extent, zoste and other alphaherpesviral infections have the highest preva lence. Staphylococcal and streptococcal diseases and scabie are also common. Drug-induced skin eruptions, which occu frequently, can create diagnostic problems.

Oral and oesophageal candidosis

Candida albicans, a yeast that is a normal commensal in the microbial flora of the skin, the oral cavity and the vagina commonly becomes pathogenic when immunological defences are suppressed by treatment or disease.

Oral candidosis is frequently the first indication of immune impairment in HIV-infected patients. It is characterized by white sloughs covering areas of superficial ulceration on the gums, palate and tongue, which contain many yeast organisms and are readily detached. In severe cases these lesions extend into the lower pharynx and oesophagus to cause dysphagia nausea and epigastric pain. Serious haemorrhage and even oesophageal perforation have occurred, but such complica tions are exceedingly rare.

Treatment

Localized lesions in the mouth generally respond to topical preparations such as oral nystatin, miconazole (250 mg every 6 hours for 10 days) or amphotericin B. Oral antiseptics with a broader spectrum of action including polyvidone–iodine and chlorhexidine also have useful anticandidal action, but they should not be swallowed, as they are toxic, particularly for infants. It may be necessary to use ketoconazole or fluconazole for treatment-resistant cases. Therapy needs to be maintained indefinitely, or prompt relapse is almost inevitable.

Oesophageal candidosis must be treated systemically. Ketoconazole is effective when oral therapy is practicable. Otherwise, amphotericin B or fluconazole must be administered by intravenous infusion. Fluconazole has also been reported to be effective in the treatment of serious candidal infections at other sites, including the lung, peritoneum and urinary tract.

Herpes simplex

Mucosal and cutaneous lesions caused by human (alpha) herpesviruses (herpes simplex viruses) 1 and 2 occur commonly among HIV-infected patients. Disseminated infection has not been reported, but occasional cases of herpesviral encephalitis, meningitis, oesophagitis and pericarditis have been recorded.

Severe primary genital lesions usually respond to oral or parenteral aciclovir but maintenance therapy must subsequently be continued indefinitely, since the condition otherwise recurs within days or weeks of termination of treatment. The emergence of resistance has recently been reported and a call has been made for screening procedures to monitor this trend.

Zoster

Zoster often supervenes months or even years before other opportunistic infections. In the later stages of HIV infection disseminated disease can occur.

Transient remission is sometimes induced by high intravenous doses of aciclovir. However, most cases resolve spontaneously and the efficacy of prolonged suppressive treatment has not been established. Treatment is consequently justified only when the disease is debilitating and there is a high risk of serious complications.

Aciclovir

Group: antiviral agent
Tablet, 200 mg, 400 mg
Powder for injection, 500 mg in vial

General information

Aciclovir, which is derived from guanine, is a synthetic purine nucleoside analogue with antiviral properties. It acts against herpesviruses by disrupting DNA synthesis and inhibiting viral replication. However, in immunocompromised patients, alphaherpesviruses are often resistant to aciclovir.

Absorption from the gastrointestinal tract is variable and incomplete. Aciclovir is widely distributed in tissues and body fluids and is excreted in the urine primarily unchanged.

Clinical information

Uses

In patients with HIV infection, treatment of:

- severe primary genital herpes
- herpesviral encephalitis
- disseminated zoster.

Dosage and administration

Intravenous infusions should be administered slowly over a period of 1 hour to avoid acute impairment of renal function.

Primary genital herpes:
5 mg/kg i.v. three times daily for 5 days.

Less severe genital infections respond to oral administration of 200 mg five times daily for 7 days.

To prevent recurrence, 400 mg may be given orally twice daily, but the optimal dosage has yet to be determined.

Herpesviral encephalitis:
10 mg/kg i.v. three times daily for 1
days.

Disseminated zoster:
10 mg/kg i.v. three times daily for
days.

Contraindications

Known hypersensitivity to purin
nucleoside analogues.

Precautions

A high fluid intake reduces the risk o
acute renal impairment.

Use in pregnancy

Aciclovir is mutagenic in anima
models. Its use in pregnancy must b
determined by the physical state of th
mother.

Adverse effects

Headache, nausea and vomiting occu
commonly after oral administration.

Transient renal impairment may occu
during intravenous therapy, possibly a
a result of crystallization in the rena
tubules. This usually responds rapidl
to dosage reduction or withdrawal o
the drug. Acute renal failure ha
responded to haemodialysis.

Overdosage

Since aciclovir is incompletely absorbe
from the gastrointestinal tract, ora
overdosage is unlikely to have seriou
sequelae. Blood concentrations can b
lowered by haemodialysis.

Storage

Tablets should be stored in tightly closed containers below 25 °C. Powder for injection should be stored at 2–8 °C. After reconstitution the solution is stable for up to 12 hours at 20 °C.

Amphotericin B

Group: antifungal agent
Powder for injection, 50 mg in vial
Lozenge, 10 mg

General information

Amphotericin B is a lipophilic polyene antibiotic that is active against protozoa and certain fungi. Since it is poorly absorbed from the gastrointestinal tract it must be administered parenterally.

It is extensively bound to lipoproteins, but it enters serous cavities and crosses the placental barrier. It is excreted unchanged in the urine over a period of several weeks.

Clinical information

Uses

In patients with HIV infection, treatment of:

- cryptococcal meningitis
- oesophageal and oral candidosis
- histoplasmosis and coccidioidomycosis.

Dosage and administration

Amphotericin B is a highly toxic substance that should be used only under experienced medical supervision. Except in the treatment of oral candidosis, the required dosages should be administered by slow intravenous infusion, when possible via a central venous catheter. An oral dose of 5 mg of hydrocortisone sodium succinate taken 1 hour before infusion of amphotericin B may reduce the severity of chills, fever and vomiting.

Infusion fluids should be freshly prepared by dissolving 50 mg in 10 ml of water for injection and making up the volume to 500 ml with 5% glucose to give a final concentration of amphotericin B of 100 µg/ml. Solutions containing electrolytes or preservatives are incompatible since they promote precipitation.

Cryptococcal meningitis:
0.5–1.0 mg/kg by i.v. infusion daily for at least 6 weeks and until cultures of cerebrospinal fluid have been negative for 4 weeks. Infusions should be continued at weekly intervals indefinitely to prevent relapse.

Oesophageal candidosis:
1 mg/kg by i.v. infusion daily for 10–14 days.

Oral candidosis:
10 mg orally four times daily after food, to be continued indefinitely. Lozenges should be retained as close to major lesions as possible and allowed to dissolve in the mouth.

Histoplasmosis and coccidioidomycosis:
0.5–1.0 mg/kg by i.v. infusion daily for at least 6 weeks, up to a maximum total dose of 3 g. Infusions of 0.5 mg/kg should be continued at weekly intervals indefinitely to prevent relapse.

Amphotericin B (continued)

Contraindications
Known hypersensitivity to amphotericin B.

Precautions
Close medical supervision is required throughout treatment.

Renal function and serum potassium concentrations should be closely monitored when high doses are administered.

A high fluid intake should be maintained. Potassium supplements may be required to compensate for urinary losses. Dosage must be reduced if renal function deteriorates substantially and particularly if serum creatinine levels rise by over 50%. Infusions of an osmotic diuretic such as mannitol may then be of value.

The blood count should be monitored at regular intervals since bone-marrow depression supervenes frequently. Occasionally, blood transfusion is required.

Use in pregnancy
Safe use during pregnancy has not been established. Amphotericin B should be used only when the need of the mother outweighs the risk of harm to the fetus.

Adverse effects
Chills, fever and vomiting are frequent during infusion. Anaphylaxis, flushing, muscle and joint pains, headache and anorexia may also occur. These effects are often most marked in the first days of treatment.

Deterioration of renal function, which may be only partially reversible, must be anticipated.

Progressive normochromic anaemia is indicative of bone-marrow suppression. Selective leukopenia and thrombocytopenia are less common.

Nerve palsies, impaired vision, tinnitus and difficult micturition have also been reported.

Drug interactions
Concomitant administration of other nephrotoxic drugs should be avoided.

Overdosage
Large doses may result in anuria, dysrhythmias, cardiac arrest, hypotension, visual disturbances and convulsions. Treatment is symptomatic. Amphotericin B cannot be removed by haemodialysis.

Storage
Vials of powder for injection should be kept in tightly closed containers protected from light. Lozenges should be stored in tightly closed containers.

Benzylpenicillins

Group: antimicrobial (penicillin) agent
Benzylpenicillin: powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (as sodium or potassium salt) in 5-ml vial
Benzathine benzylpenicillin: powder for injection, 1.44 g of benzylpenicillin (= 2.4 million IU) in 5-ml vial
Procaine benzylpenicillin: powder for injection, 1 g (= 1 million IU), 3 g (= 3 million IU) in vial

General information

Benzylpenicillin is a β-lactam antibiotic produced by *Penicillium* spp. It is bactericidal against streptococci, neisseriae, many anaerobes and spirochaetes.

After intramuscular injection, peak plasma concentrations are reached within 15–30 minutes. It is widely distributed throughout the body, has a plasma half-life of 30 minutes and is excreted mainly in the urine.

Repository formulations of benzylpenicillin are available for parenteral use. They are designed to provide a tissue depot from which the drug is slowly absorbed over a period of 12 hours to several days. Procaine benzylpenicillin produces a peak plasma concentration within 1–3 hours and is excreted over a period of several days, while benzathine benzylpenicillin takes 13–24 hours to reach its peak plasma concentration and is detectable in the urine for several weeks.

Clinical information

Uses

Treatment of:

- primary, secondary and latent syphilis of less than 2 years' duration
- late syphilis, including neurosyphilis and cardiovascular syphilis
- congenital syphilis.

Dosage and administration

Benzylpenicillin and its repository formulations must be administered parenterally.

Primary, secondary and latent syphilis of less than 2 years' duration:

benzathine benzylpenicillin 2.4 million IU i.m. in a single session, or procaine benzylpenicillin 1.2 million IU i.m. daily for 10 consecutive days.

Late syphilis (other than neurosyphilis):

procaine benzylpenicillin 1.2 million IU i.m. daily for 3 weeks, or benzathine benzylpenicillin 2.4 million IU i.m. once weekly for 3 weeks.

Neurosyphilis:

benzylpenicillin 4 million IU i.v. every 4 hours for 14 days or, provided that compliance is ensured, procaine benzylpenicillin 1.2 million IU i.m. daily for 2 weeks with oral probenecid 500 mg four times daily.

Early congenital syphilis:

Abnormal cerebrospinal fluid: benzylpenicillin 50 000 IU/kg i.m. or i.v. daily in two divided doses for 10 days, or procaine benzylpenicillin 50 000 IU/kg i.m. daily for 10 days.

Normal cerebrospinal fluid: benzathine benzylpenicillin 50 000 IU/kg i.m. as a single dose.

Benzylpenicillins (continued)

Congenital syphilis of 2 or more years' duration:
Benzylpenicillin 200 000–300 000 IU/kg i.v. daily in divided doses for 14 days (maximum 2.4 million IU daily).

Contraindications
Known hypersensitivity to penicillins or cefalosporins.

Precautions
Facilities should be available for treating anaphylaxis whenever penicillins are used. Patients should be questioned carefully about previous allergic reactions. If a skin rash develops during treatment, the patient should be transferred to a different class of antibiotic.

Use in pregnancy
Benzylpenicillin or its repository formulations can be used during pregnancy.

"Desensitization" of pregnant women with syphilis who are allergic to penicillins should not be attempted in primary care facilities.

Adverse effects
Hypersensitivity reactions range in severity from skin rashes to immediate anaphylaxis.

Pain and sterile inflammation can occur at the site of intramuscular injection; phlebitis or thrombophlebitis sometimes follows intravenous administration. Accidental injection into a peripheral nerve causes pain and dysfunction.

Rapid intravenous administration of large doses of benzylpenicillin may cause hyperkalaemia, dysrhythmias and cardiac arrest, particularly in patients with impaired renal function. Accidental intravascular administration of procaine or benzathine penicillin may produce convulsions.

Unduly high concentrations of benzylpenicillin in the brain can result in confusion, convulsions, coma and fatal encephalopathy. The procaine component has been implicated in acute mental disturbances associated with the administration of large single doses.

Interstitial nephritis, neutropenia and thrombocytopenia have been reported.

Overdosage
Overdosage can cause convulsions, paralysis and even death.

Excessive blood concentrations can be lowered by haemodialysis.

Storage
Powder for injection should be stored in vials at 2–8 °C.

Calcium folinate

Group: antidote to folinic acid antagonists
Tablet, 5 mg, 15 mg

General information

Calcium folinate is a metabolically active, reduced form of folic acid that is rapidly absorbed and extensively metabolized in the liver to other folic acid derivatives.

Clinical information

Uses

To decrease the haematopoietic toxicity of pyrimethamine and other inhibitors of folic acid metabolism in patients with HIV infection (see page 74).

Dosage and administration

Adults and children: initially, 3–5 mg orally every third day. Dosage needs to be adjusted in accordance with twice-weekly blood counts, and may exceed 15 mg every third day. Much higher doses have been administered without untoward effect.

Precautions

The possibility of pernicious anaemia should always be excluded before starting treatment with calcium folinate. Its use obscures the diagnosis by rectifying the characteristic megaloblastic anaemia but it does not prevent the neurological damage.

Use in pregnancy

Calcium folinate should always be used when pyrimethamine and sulfonamides are administered during pregnancy.

Adverse effects

Calcium folinate is generally well tolerated. Rarely, hypersensitivity reactions occur, including urticaria, rash and pruritus.

Storage

Tablets should be stored in tightly closed containers, protected from light.

Ceftriaxone

Group: antimicrobial (cefalosporin) agent
Powder for injection, 250 mg in vial

General information

Ceftriaxone is a third-generation cefalosporin derived from *Cephalosporium acremonium*. It is highly active against Gram-negative cocci and bacilli. Like benzylpenicillin, it has a β-lactam ring.

After intramuscular administration, ceftriaxone is distributed widely throughout the body. It has a relatively long plasma half-life of about 8 hours and is excreted unchanged in both urine and bile.

Clinical information

Uses

Treatment of:

- gonococcal infections
- chancroid caused by *Haemophilus ducreyi* that is resistant to β-lactams
- pelvic inflammatory disease, together with doxycycline.

Dosage and administration

Ceftriaxone must be administered parenterally.

Uncomplicated anogenital and pharyngeal gonococcal infection and gonococcal conjunctivitis in adults:
250 mg i.m. as a single dose.

Disseminated gonococcal infection:
1 g i.m. or i.v. daily for 7 days.

Neonatal gonococcal conjunctivitis:
50 mg/kg i.m. as a single dose (maximum 125 mg).

Ceftriaxone (continued)

Chancroid:
250 mg i.m. as a single dose.

Pelvic inflammatory disease:
For hospitalized patients, 250 mg i.m. twice daily together with doxycycline 100 mg orally or i.v. twice daily for 4 days (or for 48 hours after clinical improvement), followed by doxycycline 100 mg orally twice daily for 10–14 days.

Contraindications
Known hypersensitivity to other β-lactam antibiotics.

Precautions
Blood concentrations of liver enzymes may rise transiently.

Use in pregnancy
There is no evidence that ceftriaxone is teratogenic. It may be used during pregnancy.

Adverse effects
Hypersensitivity reactions are the most common adverse effects. Skin rashes are relatively frequent, while urticaria, bronchospasm and anaphylaxis are uncommon. Nausea, vomiting and diarrhoea have been reported. Rarely, antibiotic-associated pseudomembranous colitis due to *Clostridium difficile* occurs. When this is suspected treatment should be immediately discontinued.

Reversible cholestatic jaundice has been reported.

Storage
Powder for injection should be stored in tightly closed containers, protected from light.

Ciprofloxacin

Group: antimicrobial (quinolone) agent
Tablet, 250 mg (as hydrochloride)

General information

Ciprofloxacin is a synthetic quinolone that acts as a specific inhibitor of bacterial DNA-gyrase. It has a broad spectrum of efficacy against both Gram-negative and Gram-positive aerobic bacteria. Chromosomal resistance has been reported, but as yet is of little clinical significance.

Ciprofloxacin is rapidly absorbed from the gastrointestinal tract; it has a plasma half-life of 3–5 hours and is excreted in the urine mainly as unchanged drug.

Clinical information

Uses
Treatment of:

- penicillin-resistant gonorrhoea and gonococcal conjunctivitis in adults
- chancroid in patients with HI infection
- pelvic inflammatory disease, together with doxycycline and metronidazol

Dosage and administration

Uncomplicated anal and genital gonorrhoea, gonococcal conjunctivitis in adults and chancroid infections:
500 mg as a single dose.

Pelvic inflammatory disease:
For hospitalized patients, 500 mg twice daily together with doxycycline 100 mg orally twice daily and metronidazole 400–500 mg orally twice daily for 4 days (or for 48 hours after clinical improvement), followed by doxycycline 100 mg orally twice daily for 10–14 days.

Contraindications

- Hypersensitivity to any quinolone.
- Pregnancy, adolescence and childhood, since ciprofloxacin has induced arthropathy in the weight-bearing joints of young animals.

Precautions

Reduced dosage should be considered in patients with hepatic or renal impairment.

Ciprofloxacin should be administered cautiously to patients with epilepsy since seizures may be precipitated.

An adequate fluid intake must be ensured to prevent crystalluria.

Adverse effects

Ciprofloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, tremor, confusion, hallucinations, dizziness, rash and pruritus.

Myalgia, tendinitis, and hepatic and renal disturbances have also been reported.

Drug interactions

Plasma concentrations of theophylline may be raised. A prolonged bleeding time has been reported in patients receiving anticoagulants and ciprofloxacin concurrently.

Overdosage

Gastric lavage is of value if performed promptly. Electrolyte balance must be maintained. Serum concentrations of ciprofloxacin may be lowered by dialysis.

Storage

Tablets should be stored in well closed containers.

Codeine

Group: antidiarrhoeal and analgesic agent
Tablet, 30 mg of codeine phosphate

General information

Codeine is a semisynthetic methyl derivative of morphine. It is less likely to cause dependence than morphine; none the less, its supply is controlled under Schedule 1 of the Single Convention on Narcotic Drugs, 1961. It exerts its effect mainly on the central nervous system and by an antimotility effect on the bowel.

Codeine is readily absorbed after oral administration and is metabolized in the liver. The plasma half-life is 2–3 hours and it is excreted in the urine largely as inactive metabolites.

Codeine (continued)

Clinical information

Uses

In patients with HIV infection:

- treatment of mild to moderate pain
- symptomatic relief of diarrhoea.

Dosage and administration

A dose of 30–60 mg should be taken three or four times daily, as necessary.

Contraindications

- Age less than 1 year.
- Exacerbations of bronchial asthma.

Precautions

Prolonged use can result in tolerance. However, the risk of dependence is less than with other opioids.

Use in pregnancy

Codeine should be used during pregnancy only when the need outweighs any possible risk to the fetus. Its use during labour can produce respiratory depression in the infant sufficient to necessitate administration of naloxone, 10 µg/kg i.m., upon delivery.

Adverse effects

Dose-related adverse effects include nausea, dizziness and sedation.

Prolonged use can result in intractable constipation and, rarely, in paralytic ileus or toxic megacolon.

Drug interactions

Codeine potentiates the effects of other cerebral depressants.

Overdosage

Serious overdosage is characterized by respiratory depression, extreme somnolence progressing to stupor or coma and pinpoint pupils. Cardiovascular collapse and cardiac arrest are terminal events.

Supportive therapy includes mechanically assisted ventilation and administration of pressor drugs and fluids to maintain the circulating blood volume. Naloxone should be administered, as necessary, at 2-minute intervals.

Storage

Codeine tablets should be kept in tightly closed containers.

Doxycycline

Group: antimicrobial (tetracycline) agent
Capsule or tablet, 100 mg (as hyclate)
Powder for injection, 100 mg (as hyclate) in ampoule

General information

Doxycycline is a broad-spectrum antibiotic derived from and closely related to oxytetracycline. It differs from the tetracyclines in being more extensively absorbed and more lipid-soluble, and possesses a longer serum half-life that is independent of the patient's renal status.

Clinical information

Uses

Treatment of:

- *Chlamydia trachomatis* infections, including lymphogranuloma venereum

- granuloma inguinale
- syphilis in non-pregnant patients allergic to penicillin
- pelvic inflammatory disease, together with other drugs.

Dosage and administration

Chlamydia trachomatis infections:
100 mg orally twice daily for 7 days.

Lymphogranuloma venereum and granuloma inguinale:
100 mg orally twice daily for 14 days.

Syphilis (excluding neurosyphilis):
100 mg orally twice daily for 15 days. In late syphilis, treatment should be continued for a further 15 days.

Neurosyphilis:
200 mg orally twice daily for 30 days.

Pelvic inflammatory disease:
For hospitalized patients, 100 mg twice daily for 14–18 days supplemented for the first 4 days by ceftriaxone or by ciprofloxacin plus metronidazole (for routes of administration, see page 18).

Contraindications

Known hypersensitivity.

Precautions

Troublesome oesophagitis may be averted if the patient is propped up while swallowing capsules or tablets and washes them down immediately with a glass of water. Capsules and tablets should not be taken with milk or with magnesium or aluminium salts since these impair the absorption of doxycycline.

Use in pregnancy and early childhood

Doxycycline is generally contraindicated in pregnancy and during early childhood. Because it is deposited in developing teeth and bones and impairs skeletal calcification, it can result in abnormal osteogenesis and permanent staining of teeth, and occasionally causes hypoplasia of dental enamel.

Adverse effects

Gastrointestinal irritation is common and phototoxic reactions and increased vulnerability to sunburn have been reported.

Transient depression of bone growth is largely reversible, but discoloration of teeth and enamel hypoplasia are permanent.

Drug interactions

The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while taking doxycycline.

Storage

Doxycycline capsules, tablets and powder for injection should be kept in well closed containers, protected from light.

Erythromycin

Group: antimicrobial (macrolide) agent
Capsule or tablet, 250 mg (as stearate or ethyl succinate)
Powder for oral suspension, 125 mg (as stearate or ethyl succinate)
Eye ointment, 1%

General information

Erythromycin is a macrolide antibiotic produced by *Streptomyces erythreus*. It has selective bacteriostatic activity against both streptococci and staphylococci and some Gram-positive bacilli.

Because erythromycin is inactivated by gastric juices, oral formulations are protected by enteric coating. The drug diffuses rapidly into all tissues except the brain and cerebrospinal fluid. It crosses the placental barrier, and low concentrations have been reported in fetal plasma. The plasma half-life is approximately 90 minutes. Erythromycin is partially demethylated in the liver and excreted largely via the bile and faeces.

Clinical information

Uses

Treatment of:

- chancroid
- lymphogranuloma venereum, as an alternative to tetracycline
- other *Chlamydia trachomatis* infections in patients unable to take tetracycline
- neonatal chlamydial conjunctivitis
- syphilis in pregnant patients and children who are allergic to penicillin.

Dosage and administration

Erythromycin tablets should not be broken in half before administration.

Chancroid:
500 mg orally three times daily for days.

Lymphogranuloma venereum:
500 mg orally four times daily for 1 days.

Other chlamydial infections:
500 mg orally four times daily for days.

Neonatal chlamydial conjunctivitis:
50 mg/kg as syrup in four divided dose daily for 2 weeks.

Prevention of ophthalmia neonatorum:
A single application of eye ointme should be sufficient.

Syphilis:
Adults: 500 mg orally four times dai for 15 days in early syphilis and 30 da in late syphilis.

Children: 7.5–12.5 mg/kg orally fo times daily for 30 days.

The effectiveness of erythromycin syphilis is doubtful and it must be us only as a drug of last resort.

Contraindications

Known hypersensitivity to eryth mycin.

Precautions

Hepatic function should be monitor in patients with a previous history liver disease.

Use in pregnancy
Erythromycin has not been shown to be mutagenic, teratogenic or embryotoxic; it can be used during pregnancy.

Adverse effects
Nausea, vomiting and diarrhoea can occur.

Cholestatic hepatitis, which may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn.

Anaphylaxis and other hypersensitivity reactions are rare.

Drug interactions
Erythromycin, chloramphenicol and clindamycin have a similar bacteriostatic action and tend to be mutually antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.

Overdosage
Symptoms of overdosage include severe nausea, vomiting, diarrhoea and hearing loss. Induction of emesis or gastric lavage may be of value if undertaken within a few hours of ingestion.

Storage
Tablets and suspension should be stored in tightly closed containers.

Fluconazole

Group: antifungal agent
Tablet, 50 mg, 100 mg, 200 mg
Solution for injection, 2 mg/ml in ampoule

General information

Fluconazole is a fungistatic triazole derivative that is particularly effective against *Cryptococcus neoformans*. It is well absorbed and passes readily across the blood–brain barrier into the cerebrospinal fluid. It is slowly eliminated unchanged in the urine.

Clinical information

Uses
In patients with HIV infection:

- treatment and prophylaxis of cryptococcal meningitis
- treatment of oesophageal and resistant oropharyngeal candidosis, vaginal candidosis and serious systemic candidal infections, in particular of the urinary tract, peritoneum and lungs.

Dosage and administration

Cryptococcal meningitis:
An oral or i.v. dose of 400 mg is effective if taken daily for at least 12 weeks after cultures from the cerebrospinal fluid become negative. Suppressive treatment with a daily dose of 200 mg should then be continued indefinitely.

Oesophageal and resistant oropharyngeal candidosis:
200 mg as an initial loading dose, followed by 100 mg daily for 21 days (i.v. administration for oesophageal candidosis).

Fluconazole (continued)

Vaginal candidosis:
150 mg as a single oral dose.

Systemic candidosis:
400 mg orally or i.v. as an initial loading dose, followed by 200 mg daily for at least 4 weeks.

Contraindications
Hypersensitivity to azole derivatives.

Precautions
Dosage should be reduced in accordance with the creatinine clearance rate in patients with renal impairment.

Use in pregnancy
Safe use in pregnancy has not been established. The need for treatment must be determined by the condition of the mother.

Adverse effects
Fluconazole is generally well tolerated. Nausea is the most frequently reported adverse effect. Vomiting and abdominal distension and discomfort are also reported.

Elevation of hepatic enzyme levels, which occurs in a small percentage of individuals, is readily reversible in the early stages. Treatment should be discontinued if signs develop that are suggestive of hepatic disease.

Fluconazole should be withdrawn if skin rashes progress during treatment. Exfoliative skin disorders have been reported, but a causal association has not been established.

Drug interactions
The hepatic metabolism of other lipid-soluble drugs, such as ciclosporin, phenytoin, sulfonylureas, theophylline and warfarin, is inhibited.

Rifampicin accelerates the clearance of fluconazole.

Concomitant administration of terfenadine should be avoided since it has been associated with serious, sometimes fatal cardiac dysrhythmias.

Overdosage
No experience has been gained with overdosage of fluconazole. Induction of emesis and gastric lavage may be tried in the case of accidental overdosage.

Storage
Tablets should be kept in well closed containers, protected from light. Intravenous preparations should be stored in well closed containers and should not be allowed to freeze.

Ganciclovir

Group: antiviral agent
Powder for injection, 500 mg in vial

General information

Ganciclovir is an acyclic nucleoside analogue of guanine that acts as an antiviral agent by disrupting DNA synthesis and inhibiting viral replication. It is used specifically to treat serious cytomegalovirus infections. It is also active against the herpesviruses but is too toxic to be of practical value in this regard.

After intravenous infusion ganciclovir readily penetrates into the brain and

subretinal fluids. It has a plasma half-life of 3–4 hours and is excreted primarily in the urine.

Clinical information

Uses
Treatment of cytomegalovirus infections that threaten life or sight in patients with HIV infection.

Dosage and administration
A dose of 5 mg/kg should be given by slow intravenous infusion every 12 hours for the first 14–21 days. Maintenance treatment with 5 mg/kg daily should then be continued indefinitely.

Contraindications
Known hypersensitivity to purine nucleoside analogues.

Precautions
Dosage should be adjusted in accordance with the creatinine clearance rate in patients with impaired renal function.

The blood count should be monitored every 2 days for the first 14 days. Particular vigilance is required when ganciclovir is administered in combination with other myelosuppressive drugs, such as zidovudine, pentamidine and sulfamethoxazole/trimethoprim.

Use in pregnancy
Because of the urgent need to treat cytomegalovirus infections, ganciclovir should not be withheld during pregnancy.

Adverse effects
The most common severe adverse effects are anaemia, leukopenias (especially neutropenia) and thrombocytopenia. Fever, rash, abnormal liver function tests, raised blood urea concentrations, behavioural changes, psychosis, convulsions and coma sometimes occur.

Drug interactions
Concomitant administration of zidovudine and other myelosuppressive drugs has been associated with severe haematological abnormalities.

Overdosage
Overdosage causes bone-marrow depression. Management is largely supportive; haemodialysis may be of value.

Storage
Vials of powder for injection should be stored below 25 °C. Infusion solutions may be stored for up to 24 hours at 4 °C.

Ketoconazole

Group: antifungal agent
Tablet, 200 mg
Oral suspension, 100 mg/5 ml

General information

Ketoconazole is a synthetic imidazole derivative with fungistatic activity against a wide range of organisms. It is rapidly absorbed from the gastrointestinal tract and is partially metabolized in the liver. It is largely excreted in the faeces via the bile.

Ketoconazole (continued)

Clinical information

Uses

Treatment of oesophageal and resistant oropharyngeal candidosis in patients with HIV infection.

Dosage and administration

Oesophageal candidosis:
200–400 mg daily until remission is obtained. The need for subsequent maintenance doses of 200 mg daily should be considered.

Resistant oropharyngeal candidosis:
200 mg once daily until remission is obtained.

Children > 2 years:
3–6 mg/kg daily.

Contraindications

- Hypersensitivity to azole derivatives.
- Impaired hepatic function.
- Chronic alcohol dependence.
- Age less than 2 years.

Precautions

Liver function should be assessed before and at monthly intervals throughout treatment.

Use in pregnancy

Ketoconazole is fetotoxic in animals. Its use in pregnancy must be determined by the physical state of the mother.

Adverse effects

Anaphylactic reactions have been reported following the first dose. Hypersensitivity may also present as pruritus, purpura or urticaria.

Nausea, vomiting, abdominal pain, constipation, diarrhoea and transient increases in plasma concentrations of hepatic enzymes are common. Treatment should be withdrawn immediately if there is evidence of more severe hepatocellular damage.

Gynaecomastia and menstrual irregularities have also been reported.

Drug interactions

Absorption of ketoconazole from the gastrointestinal tract is pH dependent. Concomitant administration of drugs that reduce gastric acid secretion, such as histamine H_2-receptor antagonists, and of other antacids should be avoided whenever possible.

Ketoconazole's extensive binding to plasma proteins and induction of hepatic enzymes are responsible for certain drug interactions. The anticoagulant effect of coumarin compounds may be enhanced, and use of ketoconazole with rifampicin or ciclosporin may alter the metabolism of one or both drugs. Ketoconazole should not be administered concomitantly with either astemizole or terfenadine, as cardiac irregularities including prolonged Q–T intervals and ventricular fibrillation may occur.

Overdosage

Induction of emesis or gastric lavage should be undertaken in the event of overdose.

Storage

Ketoconazole tablets should be kept in well closed containers.

Metronidazole

Group: antiprotozoal agent
Tablet, 200 mg, 250 mg, 400 mg, 500 mg
Oral suspension, 200 mg (as benzoate)/5 ml

General information

Metronidazole is a 5-nitroimidazole derivative with antimicrobial activity against anaerobic bacteria and certain protozoa, including *Trichomonas vaginalis*. It is almost completely absorbed after oral administration. Its plasma half-life is about 8 hours and it is excreted largely in the urine, both unchanged and as metabolites.

Clinical information

Uses

Treatment of:

- confirmed trichomoniasis in adults
- trichomoniasis in neonates persisting for more than 4 weeks
- vaginosis due to *Gardnerella vaginalis*
- pelvic inflammatory disease, together with ciprofloxacin and doxycycline.

Dosage and administration

Metronidazole should preferably be administered with or immediately after meals.

Trichomoniasis:

Adults: 2 g as a single dose, or 400–500 mg twice daily for 7 days.

Infants more than 4 weeks old: 15 mg/kg daily for 5 days in divided doses.

Gardnerella vaginalis infections:

Adults: 400–500 mg twice daily for 7 days.

Pelvic inflammatory disease:

For hospitalized patients, 400–500 mg twice daily together with ciprofloxacin 500 mg orally twice daily and doxycycline 100 mg orally twice daily for 4 days (or for 48 hours after clinical improvement), followed by doxycycline 100 mg orally twice daily for 10–14 days.

Contraindications

- Known hypersensitivity.
- Early pregnancy.
- Chronic alcohol dependence.

Precautions

Patients should be warned not to take any alcohol during treatment since disulfiram-like reactions can occur.

Use in pregnancy and lactation

Metronidazole should not be used to treat trichomoniasis during early pregnancy. For symptomatic relief, clotrimazole 100 mg may be given as a vaginal suppository daily for 7 days. Breast-feeding should be interrupted until 24 hours after cessation of treatment since metronidazole is excreted in milk.

Adverse effects

In general, metronidazole is well tolerated, but mild symptoms of headache, gastrointestinal irritation and a persistent metallic taste are common. Less frequently, drowsiness, rashes and darkening of urine occur.

More serious reactions are rare and usually occur only during extended courses of treatment. They include stomatitis and candidosis, reversible leukopenia, and sensory peripheral neuropathy, which is usually mild and rapidly reversible.

Metronidazole (continued)

Ataxia and epileptiform seizures have been reported among patients receiving dosages considerably higher than those currently recommended.

Drug interactions

The action of oral anticoagulants is potentiated. Alcohol may induce abdominal pain, vomiting, flushing and headache.

Phenobarbital and corticosteroid lower plasma levels of metronidazole whereas cimetidine raises them.

Overdosage

No specific treatment exists. Emesis o gastric lavage may be of value within few hours of ingestion.

Storage

Tablets and suspension should be kep in well closed containers, protecte from light.

Miconazole

Group: antifungal agent
Cream, 2% (20 mg/ml) miconazole nitrate

General information

Miconazole is a synthetic imidazole active against fungi (both dermatophytes and yeasts) and Gram-positive cocci (*Staphylococcus* and *Streptococcus* spp.).

Clinical information

Uses

Treatment of vaginal candidosis.

Dosage and administration

A dose of 10 ml (200 mg) of cream should be inserted high into the vagina on 3 consecutive nights.

Contraindications

- Known hypersensitivity to miconazole.
- Severe liver impairment.

Precautions

Treatment should be discontinued irritation or sensitivity occurs. Mic nazole should not come in contact wi the eyes.

Use in pregnancy

Topically applied miconazole is n systemically absorbed and can be use safely during pregnancy and lactation

Adverse effects

Isolated cases of sensitization have bee reported, characterized by irritation an burning and necessitating disconti uation of treatment.

Storage

Cream should be stored in a cool plac protected from light.

Nystatin

Group: antifungal agent
Tablet, 500000IU
Pessary, 100000IU

General information

Nystatin is an antifungal polyene antibiotic derived from *Streptomyces noursei*. It is effective against infections caused by a wide range of yeasts and yeast-like fungi.

Clinical information

Uses

- Treatment of vaginal candidosis.
- Treatment and prevention of oral candidosis in patients with HIV infection.

Dosage and administration

Vaginal candidosis:
100000–1000000IU as pessaries inserted high into the vagina nightly for at least 2 weeks.

Administration should be continued for 48 hours after clinical cure. Higher doses and a longer period of treatment may be necessary in immunocompromised patients.

Oral candidosis in patients with HIV infection:
Treatment: one tablet four times daily; tablets should be sucked, not swallowed, and retained in the mouth for as long as possible. Therapy should be continued for at least 48 hours after symptoms have resolved.

Prophylaxis: two tablets daily, to be continued indefinitely.

Contraindications and precautions

Treatment should be discontinued if symptoms of irritation or sensitization occur.

Use in pregnancy

Safe use in pregnancy has not been established. The need for treatment must be determined by the condition of the mother.

Adverse effects

Mild and transient nausea, vomiting and diarrhoea may occur after oral administration. Irritation rarely occurs after topical application.

Storage

Tablets should be stored in well closed containers. Pessaries should be stored below 15°C in well closed containers, protected from light.

Pentamidine

Group: antiprotozoal agent
Powder for injection, 200 mg of pentamidine isetionate in vial
Powder for inhalation (aerosol), 300 mg of pentamidine isetionate in vial

General information

Pentamidine is a stable diamidine compound with antiprotozoal activity that is administered parenterally because it is absorbed unreliably from the gastrointestinal tract. It does not enter the cerebrospinal fluid. Detectable amounts remain in the liver and kidney for many months as a result of selective binding. Excretion occurs mainly in the bile; a small fraction is excreted unchanged in the urine within 24 hours.

Clinical information

Uses

Treatment and prophylaxis of pneumonia due to *Pneumocystis carinii* in patients with HIV infection.

Dosage and administration

Treatment:
4 mg/kg by i.v. infusion over at least 60 minutes, daily for at least 3 weeks.

For patients with severe renal failure, infusions should be administered on alternate days.

Prophylaxis:
300 mg in 6 ml by oral inhalation as a single dose every 4 weeks, to be continued indefinitely. The nebulizer should provide a particle size of less than 5 μm.

Contraindications

Known hypersensitivity to pentamidine.

Precautions

Because of the risk of hypotension and syncope all patients should remain supine and under observation for at least 30 minutes after each injection.

The risk of death during the first few days of treatment can be substantially reduced if a corticosteroid is administered as soon as therapy is started, if the patient's arterial oxygen tension is less than 70 mmHg (9.33 kPa).

Blood pressure, blood count and serum creatinine and blood glucose concentrations should be monitored daily throughout treatment.

Interruption or discontinuation of treatment may need to be considered should acute deterioration of bone marrow, renal or pancreatic function occur.

Use in pregnancy

Use in pregnancy can induce abortion. However, pneumonia due to *Pneumocystis carinii* must always be treated without delay.

Adverse effects

Mild nephrotoxicity is frequent and usually completely reversible.

Rapid intravenous infusion can induce acute hypotension and syncope. Oral inhalation can precipitate bronchospasm.

Pancreatic damage firstly induces hypoglycaemia due to excessive insulin release. Hyperglycaemia due to insulin insufficiency and pancreatitis may occur subsequently.

Other adverse effects include hypocalcaemia, gastrointestinal effects, confusion, hallucinations, cardiac dysrhythmias, local induration and, occasionally, sterile abscess formation. Rarely, thrombocytopenia, leukopenia, abnormal hepatic function tests and erythema multiforme (Stevens–Johnson syndrome) have been reported.

Storage

Vials of dry powder should be stored below 30 °C. Dilute solutions should be stored at 2–8 °C and any unused portion should be discarded within 24 hours of preparation.

Podophyllum resin

Group: keratolytic agent
Solution, 10–25%

General information

Podophyllum resin is a powdered mixture of resins extracted from the roots of *Podophyllum peltatum*. A solution is prepared by forming a paste with benzoin in alcohol. It is a caustic keratolytic agent for topical application.

Clinical information

Uses

Topical treatment of genital warts (condylomata acuminata).

Dosage and administration

A 10–25% solution should be applied to the affected area. Care must be taken to avoid contact with normal tissue. The solution should be thoroughly rinsed off after 1–4 hours.

Therapy may be repeated at weekly intervals up to a maximum of four applications.

The active ingredient podophyllotoxin (0.5%) is available in some countries. It is less corrosive and may be applied without medical supervision.

Contraindications

Podophyllum resin should not be applied to large areas of skin, nor should it be used in the treatment of cervical, urethral, anorectal or oral warts.

Treatment is contraindicated during pregnancy since podophyllum resin is both teratogenic and fetotoxic.

Precautions

Preparations of podophyllum resin should be used only under close medical supervision because potentially serious local and systemic toxic effects can result from prolonged or excessive applications. Systemic absorption is enhanced when applications are made to friable, bleeding warts.

Adverse effects

The systemic effects of excessive cutaneous absorption include nausea, vomiting, abdominal pain and diarrhoea.

Transient leukopenia and thrombocytopenia sometimes occur, providing evidence of bone-marrow depression.

Gross over-application can result in serious neurotoxicity. The signs are

Podophyllum resin (continued)

characteristically delayed in onset and slow to resolve. They include visual and auditory hallucinations, delusions, disorientation, confusion and delirium.

Storage

Topical solution should be kept in tightly closed containers, protected from light and excessive heat. The shelf-life of the resin is variable and some formulations may begin to degrade within a few days of exposure to light, air or heat.

Pyrimethamine

Group: antiprotozoal agent
Tablet, 25 mg, 50 mg

General information

Pyrimethamine is an inhibitor of folic acid metabolism that acts synergistically with sulfonamides to kill *Toxoplasma gondii* tachyzoites. The high dosages required may also interfere with folic acid metabolism in the host.

The plasma half-life after oral administration is about 4 days. Pyrimethamine is partially metabolized in the liver and ultimately excreted in the urine.

Clinical information

Uses

Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis in patients with HIV infection.

Dosage and administration

A total of 200 mg in divided doses on the first day, followed by 75–100 mg daily for at least 6 weeks. Suppressive treatment with a daily dose of 25–50 mg should then be continued indefinitely.

Pyrimethamine at this dosage must *always* be taken together with sulfadiazine. Daily dosages for the latter are set out on page 76.

Pyrimethamine has been administered alone to patients who are hypersensitive to sulfonamides at dosages some four times those suggested here. However such regimens are associated with a greater risk of bone-marrow depression.

Contraindications

- Known hypersensitivity to pyrimethamine.
- Severe hepatic or renal dysfunction.
- Pregnancy during the first trimester except when the mother's health is seriously endangered.

Precautions

All patients should receive calcium folinate concurrently to prevent folinic acid deficiency resulting from high daily doses of pyrimethamine (for dosage details, see page 59).

Use in pregnancy

Pyrimethamine is normally contra-indicated during the first trimester, but administration should not be delayed when the mother's health is seriously endangered. It should always be given thereafter to reduce the risk of congenital transmission.

Adverse effects
Anorexia, abdominal cramps, vomiting, ataxia, tremors and seizures have been reported.

At the high dosages required for the treatment of toxoplasmosis, pyrimethamine may induce thrombocytopenia, granulocytopenia and a megaloblastic anaemia due to folinic acid deficiency.

Drug interactions
Various other drugs, including all sulfonamides, trimethoprim and methotrexate, act synergistically with pyrimethamine to inhibit folic acid metabolism. Coadministration (other than planned use of sulfadiazine) should be avoided.

Overdosage
Excessive doses of pyrimethamine are potentially fatal and induce anorexia, vomiting and seizures. Induction of emesis or gastric lavage is of value when undertaken within a few hours of ingestion. Convulsions may be controlled with parenteral diazepam.

Storage
Tablets should be kept in well closed containers, protected from light and moisture.

Spectinomycin

Group: antimicrobial agent
Powder for injection, 2g (as hydrochloride) in vial

General information

Spectinomycin is produced from *Streptomyces spectabilis*. It is most effective against *Neisseria gonorrhoeae*, in which it selectively inhibits protein synthesis.

It is rapidly absorbed after intramuscular injection and peak plasma concentrations occur after 1 hour. It is not significantly bound to plasma proteins and is excreted unchanged in the urine.

Clinical information

Uses
Treatment of:

- uncomplicated anogenital and disseminated gonorrhoea
- adult and neonatal gonococcal conjunctivitis
- chancroid, as an alternative to erythromycin.

Dosage and administration

Uncomplicated anogenital gonorrhoea:
2g i.m. as a single dose.

Disseminated gonococcal infections:
2g i.m. twice daily for 7 days.

Gonococcal conjunctivitis:
Adults: 2g i.m. as a single dose.

Neonates: 25mg/kg as a single dose (maximum 75mg).

Chancroid:
2g i.m. as a single dose.

Contraindications
Known hypersensitivity.

Spectinomycin (continued)

Precautions
In patients with renal impairment, spectinomycin should be used only when alternative therapies are inappropriate.

Use in pregnancy
Since safety in pregnancy has not been established, spectinomycin should be used in pregnant women only if the need outweighs any possible risk to th fetus.

Adverse effects
Hypersensitivity reactions occur rarel

Pain at the injection site, nausea, feve dizziness and urticaria have be reported.

Storage
Powder for injection should be stored vials.

Sulfadiazine

Group: antimicrobial agent
Tablet, 500 mg
Solution for injection, 250 mg/ml in ampoule

General information

Sulfadiazine is an inhibitor of folic acid metabolism in bacteria and protozoa that acts synergistically with pyrimethamine.

Sulfadiazine is rapidly absorbed from the gastrointestinal tract and widely distributed in the body. The serum half-life is about 10–12 hours. After partial acetylation in the liver it is excreted in the urine.

Clinical information

Uses
Treatment of:

- toxoplasmic encephalitis and other manifestations of active toxoplasmosis in patients with HIV infection
- lymphogranuloma venereum.

Dosage and administration

Toxoplasmosis in patients with HIV infection:
A total of 6–8 g orally or i.v. in four divided doses daily for at least 6 wee followed by a suppressive dose of 2– daily, to be continued indefinitely.

For the treatment of toxoplasmos sulfadiazine must always be adm istered in combination with pyrime amine (see page 74).

Lymphogranuloma venereum:
1 g orally four times daily for 7 days.

Contraindications
- Known hypersensitivity to sulfo mides.
- Pregnancy during the first trimes except when the mother's health seriously endangered.
- Severe hepatic or renal dysfunctio

Precautions
Patients with HIV infection receiv sulfadiazine and pyrimethamine tr ment for toxoplasmosis should be gi calcium folinate concurrently to prev folinic acid deficiency (for dos details, see page 59).

In these patients, the blood count should be monitored twice weekly throughout therapy to detect signs of bone-marrow depression. Administration should be discontinued immediately should presumptive signs of hypersensitivity occur, such as skin rashes, dark urine and purpura.

Sulfadiazine is less soluble in urine than many other sulfonamides. A high output of alkaline urine must be maintained during treatment of toxoplasmosis to avoid crystallization.

In all patients, concomitant administration of other drugs that interfere with folic acid metabolism (apart from pyrimethamine) should be avoided whenever possible.

Use in pregnancy

Administration of sulfonamides during pregnancy can induce severe hypersensitivity reactions in the mother. Their action in displacing bilirubin from protein-binding sites has given rise to concern, based on data derived from premature neonates, that they may promote kernicterus. Although sulfonamides readily cross the placental barrier there is no conclusive evidence that the fetus is at risk. Nevertheless, sulfadiazine should not be administered during the first trimester, except when the mother's health is seriously endangered.

Adverse effects

Nausea, vomiting, diarrhoea and headache sometimes occur.

Sulfonamide-induced hypersensitivity reactions can be severe. They include rare life-threatening cutaneous reactions such as erythema multiforme (Stevens–Johnson syndrome) and toxic epidermal necrolysis.

Crystalluria may result in dysuria, renal colic, haematuria and acute renal obstruction.

Other infrequent reactions include granulocytopenia, thrombocytopenic purpura, agranulocytosis, aplastic anaemia and toxic hepatitis. Haemolysis occasionally occurs in individuals deficient in glucose-6-phosphate dehydrogenase.

Overdosage

Continuous forced diuresis may be beneficial and an alkaline urine should be maintained. Treatment is otherwise symptomatic.

Storage

Tablets should be kept in well closed containers, protected from light. Solution for injection should be kept in ampoules.

Sulfamethoxazole/trimethoprim

Group: antimicrobial agent
Tablet, 100 mg of sulfamethoxazole + 20 mg of trimethoprim, 400 mg + 80 mg, 800 mg + 160 mg
Concentrate for i.v. infusion, 400 mg + 80 mg in 5-ml ampoule
Oral suspension, 200 mg + 40 mg in 5 ml

General information

The two components of this combination product have a similar antimicrobial spectrum and both have antiprotozoal activity. They operate synergistically because they independently inhibit different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible organisms.

Trimethoprim is absorbed more rapidly, is more widely distributed in tissues, and enters the cerebrospinal fluid more quickly than sulfamethoxazole. Both compounds are moderately bound to plasma proteins, and each is excreted largely unchanged in the urine at a rate that gives a plasma half-life of about 12 hours.

Clinical information

Uses

- Treatment of granuloma inguinale.
- Treatment of chancroid (as an alternative to erythromycin) and gonorrhoea in areas where strains remain sensitive and regular monitoring can be carried out.
- Treatment and prophylaxis of pneumonia due to *Pneumocystis carinii* in patients with HIV infection.

Dosage and administration

Granuloma inguinale:
Sulfamethoxazole 800 mg + trimethoprim 160 mg orally twice daily for 14 days.

Chancroid:
Sulfamethoxazole 800 mg + trimethoprim 160 mg orally twice daily for 7 days.

Gonorrhoea:
Sulfamethoxazole 4000 mg + trimethoprim 800 mg orally as a single dose once daily for 3 days.

Pneumonia due to Pneumocystis carinii in patients with HIV infection

Treatment
Oral administration: sulfamethoxazole 100 mg/kg + trimethoprim 20 mg/kg in two to four divided doses daily for at least 3 weeks.

Intravenous infusion for severely ill patients: sulfamethoxazole 75 mg/kg + trimethoprim 15 mg/kg daily in four divided doses, each administered in 5% glucose solution in water over 60 minutes. Oral dosage forms should be substituted as soon as they can be ingested.

Prophylaxis
Sulfamethoxazole 25 mg/kg + trimethoprim 5 mg/kg in two divided doses daily on 3 consecutive days each week for as long as immunosuppression persists.

Contraindications

- Known hypersensitivity.
- Severe hepatic or renal dysfunction.

Precautions

n HIV-infected patients with pneumo-
ia due to *Pneumocystis carinii* whose
rterial oxygen tension is less than
0mmHg (9.33kPa), the risk of death
luring the first few days of treatment
an be substantially reduced if a
orticosteroid is administered as soon as
herapy is started.

reatment should be suspended
mmediately should a rash or any other
anifestation of sulfonamide hyper-
ensitivity occur.

he risk of sulfonamide crystalluria is
ecreased by maintaining a daily
rinary output of at least 1.5 litres.
henever possible, plasma sulfona-
ide concentrations should be deter-
ined periodically.

atients must be advised to seek
edical advice should they develop a
ore throat or fever during treatment.
his advice can be of greater value than
outine monitoring of the white cell
ount.

ince elderly patients may be more
usceptible to severe adverse reactions,
specially blood dyscrasias, their
eatment should not be unnecessarily
rolonged.

atients deficient in folate may require
upplementary calcium folinate to
revent megaloblastic anaemia.

se in pregnancy

he combination of sulfamethoxazole
d trimethoprim is best avoided in
regnancy as it may give rise to
ernicterus of the newborn. However,
eatment of patients with *Pneumocystis*
rinii pneumonia, which is life-
reatening, should in no circumstance
e delayed.

dverse effects

ausea, vomiting, glossitis and skin rashes are common. In patients with HIV infection receiving sulfamethoxazole/trimethoprim for *Pneumocystis carinii* pneumonia, recurrent fever, neutropenia, thrombocytopenia and increases in serum transaminase levels also occur frequently.

Trimethoprim may induce a megaloblastic anaemia responsive to calcium folinate.

Sulfonamide-induced hypersensitivity reactions can be severe. They include life-threatening cutaneous reactions such as erythema multiforme (Stevens–Johnson syndrome) and toxic epidermal necrolysis.

Other reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Haemolysis occasionally, occurs in individuals deficient in glucose-6-phosphate dehydrogenase.

Drug interactions

Maintenance requirements for sulfonylureas and coumarin anticoagulants are often reduced as a result of their displacement from plasma proteins by sulfamethoxazole.

Concomitant use of other inhibitors of folate metabolism (such as pyrimethamine, methotrexate and certain anticonvulsants) increases the risk of megaloblastic anaemia.

Overdosage

Symptoms of acute overdosage include vomiting, dizziness and confusion followed by visual disturbances, petechiae, purpura and jaundice. Crystalluria, haematuria and anuria may also occur.

Emesis or gastric lavage may be of value within a few hours of ingestion. Provided urinary output is satisfactory, a high fluid intake should be

Sulfamethoxazole/trimethoprim (cont.)

maintained. Haemodialysis may be of value in eliminating some of the drug. Otherwise, treatment is symptomatic and supportive.

Storage

Tablets, oral suspension and concen trate for infusion should be stored protected from light, in well close containers.

Tetracycline

Group: antimicrobial (tetracycline) agent
Capsule or tablet, 250 mg of tetracycline hydrochloride
Eye ointment, 1% tetracycline hydrochloride

General information

Tetracycline is a broad-spectrum antibiotic derived from a species of *Streptomyces*. It induces bacteriostasis by inhibiting protein synthesis, and is selectively concentrated in susceptible organisms.

Absorption occurs mainly from the stomach and small intestine. Peak plasma concentrations occur within 4 hours and decay with a half-life of about 8 hours. Excretion is primarily effected by filtration into the urine. Entero-hepatic circulation results in high concentrations of tetracycline accumulating in the liver and bile. Bacteriostatic concentrations are maintained for up to 6 hours after topical administration.

Tetracycline crosses the placenta and is excreted in breast milk.

Clinical information

Uses

Treatment of:

- *Chlamydia trachomatis* infections, including lymphogranuloma venereum
- granuloma inguinale
- syphilis in non-pregnant patients a lergic to penicillin.

Prevention and (when systemic trea ment is not available) treatment of co junctivitis of the newborn due *Neisseria gonorrhoeae* and *Chlamyd trachomatis*.

Dosage and administration

Chlamydia trachomatis infections:
500 mg orally four times daily for days.

Lymphogranuloma venereum and granuloma inguinale:
500 mg orally four times daily for days.

Syphilis:
500 mg orally four times daily for days. In neurosyphilis and late syphi treatment should be continued for further 15 days.

Ophthalmia neonatorum:
Prevention: a single application of ointment should be sufficient.

Treatment: ointment should be instil into each eye hourly pending referra the infant.

Contraindications

- Known hypersensitivity.

Severe renal impairment.
Pregnancy and early childhood (except for topical use to prevent or treat ophthalmia neonatorum).

recautions

roublesome oesophagitis may be verted if the patient is propped up vhile swallowing capsules or tablets nd washes them down immediately vith a glass of water. Capsules and ablets should not be taken with milk or vith magnesium or aluminium salts ince these impair the absorption of etracycline.

ime-expired capsules and tablets hould be discarded. Degraded etracycline has been reported to induce enal dysfunction indistinguishable rom the Fanconi syndrome and skin esions similar to those of systemic upus erythematosus.

se in pregnancy and early hildhood

etracycline is generally contraindiated in pregnancy and during early hildhood. Because it is deposited in leveloping teeth and bones and impairs keletal calcification, it can result in bnormal osteogenesis and permanent taining of teeth, and occasionally auses hypoplasia of dental enamel.

Adverse effects

Gastrointestinal irritation is common, as is depletion of the normal bowel flora, permitting overgrowth of resistant organisms. Irritative diarrhoea should be differentiated from enteritis due to suprainfection, particularly with coagulase-positive staphylococci, and from pseudomembranous colitis due to *Clostridium difficile*.

Phototoxic reactions occasionally result in porphyria-like skin changes and pigmentation of the nails.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis have been reported, as have angioedema, anaphylaxis and pseudotumour cerebri.

Drug interactions

The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while taking tetracyclines.

Storage

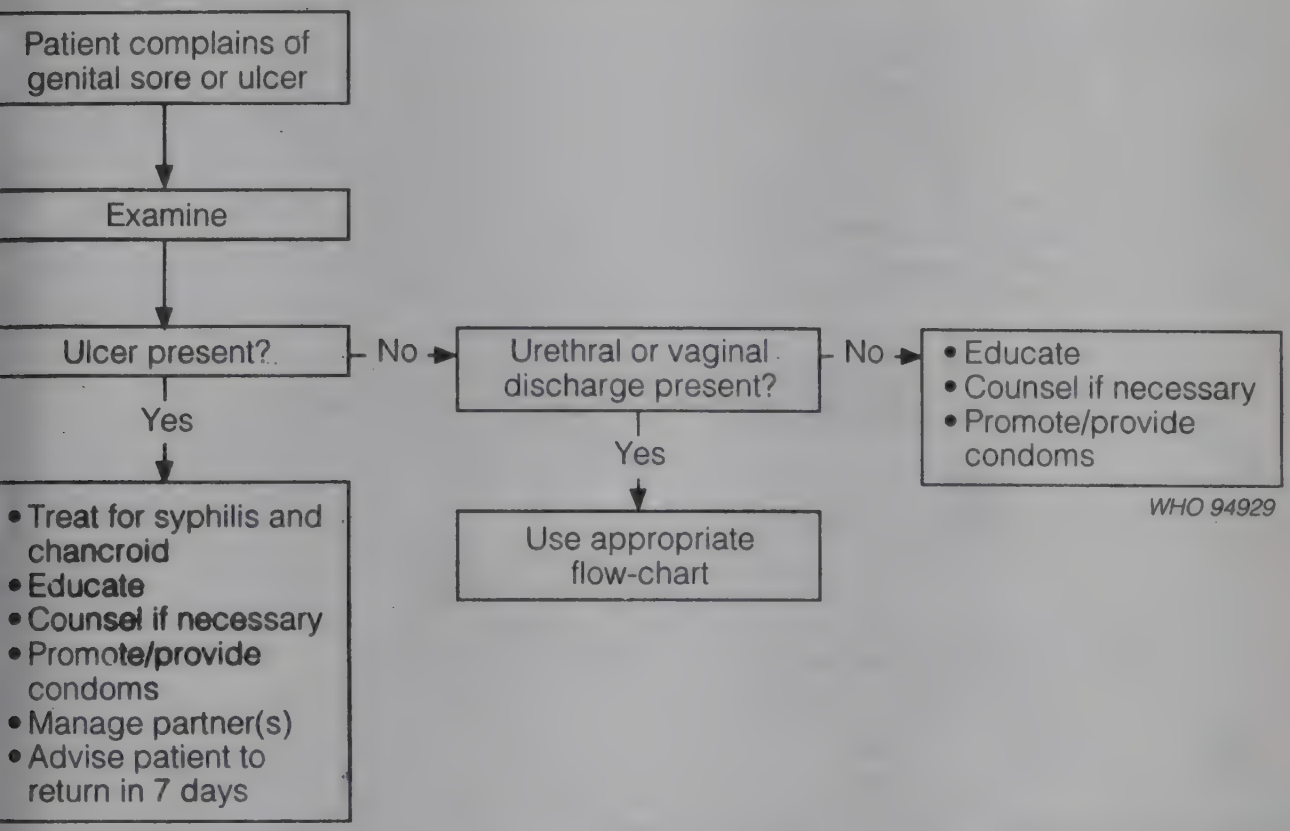
Tetracycline capsules, tablets and ointment should be kept in well closed containers, protected from light.

Flow-charts for the management of commonly encountered syndromes

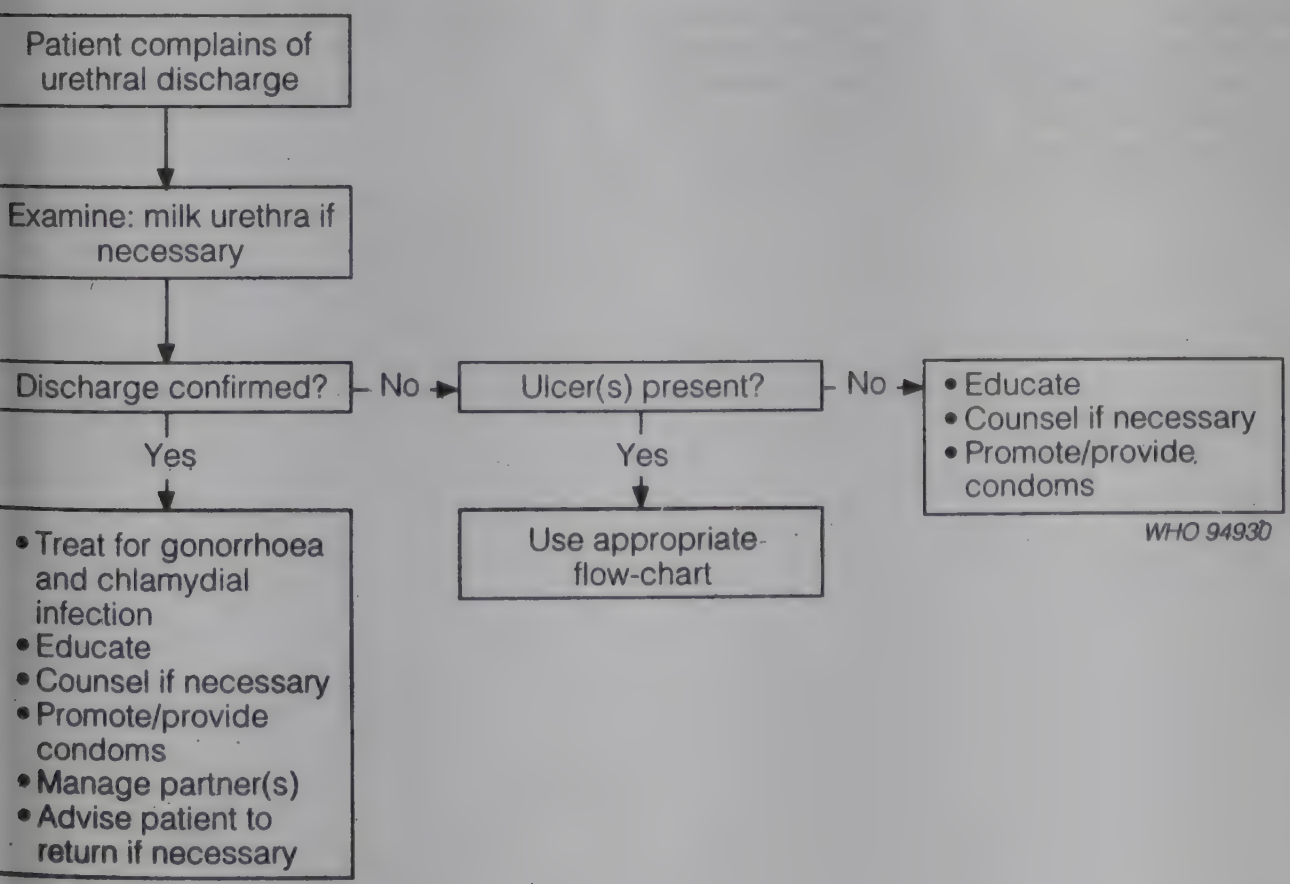
A fundamental problem in the management of most sexuall transmitted diseases is the difficulty in making an accurat diagnosis. Even in countries where sophisticated laborator facilities are available, it is often not possible to make an accu rate diagnosis when a patient with a sexually transmitted dis ease first presents for treatment. The following flow-charts ar intended to assist all health workers in the empirical manage ment of the most commonly encountered syndromes. The should not replace clinical judgement nor do they obviate th need for confirmatory testing and screening where the labora tory facilities are available.

Health workers should, at the first encounter with a patie with a sexually transmitted disease, take the opportunity t provide information on the prevention of disease, includin the use of condoms, and on the importance of notifying an treating sexual partner(s). They should also provide counse ling, if necessary, for example to help a patient to cope wit HIV infection. Further information on these matters can b found in related WHO publications, for example *Manageme of patients with sexually transmitted diseases. Report of a WH Study Group.* (WHO Technical Report Series, No. 810, 1991 which draws attention to the practical issues in risk-reductio counselling, principles of confidentiality and cultural and leg aspects of partner notification, and *AIDS in Africa: a manual f physicians* (Piot P et al., 1992), which includes a chapter o counselling and psychosocial support for patients with HI infection.

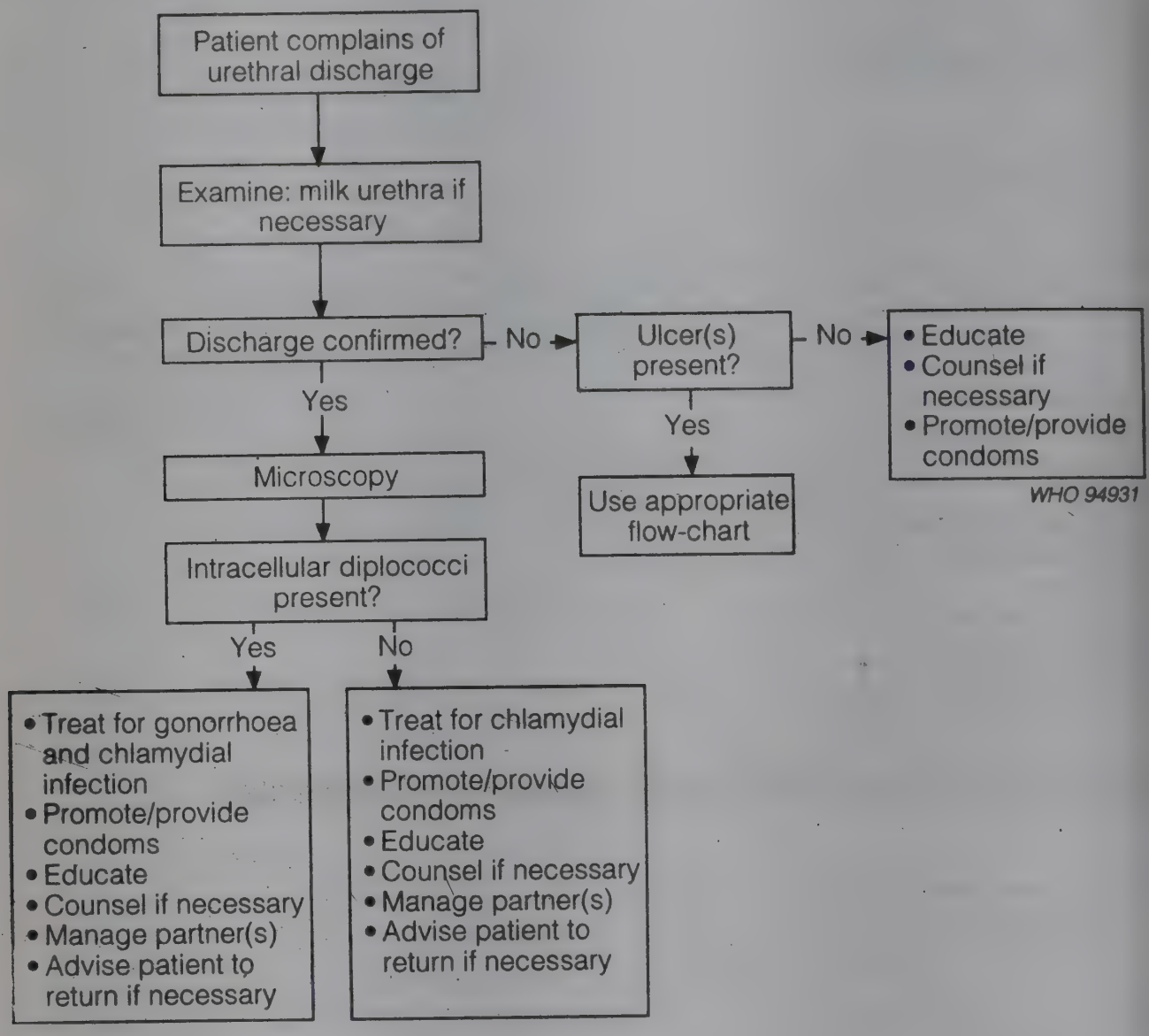
Genital ulcers (laboratory support not available)



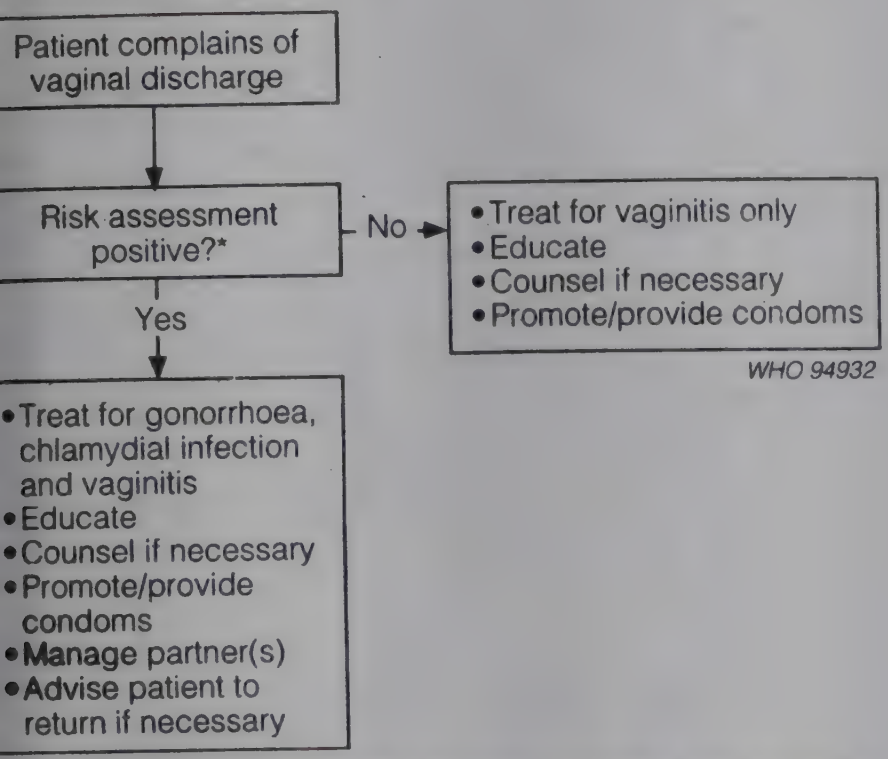
Urethral discharge (laboratory support not available)



Urethral discharge (microscope available)

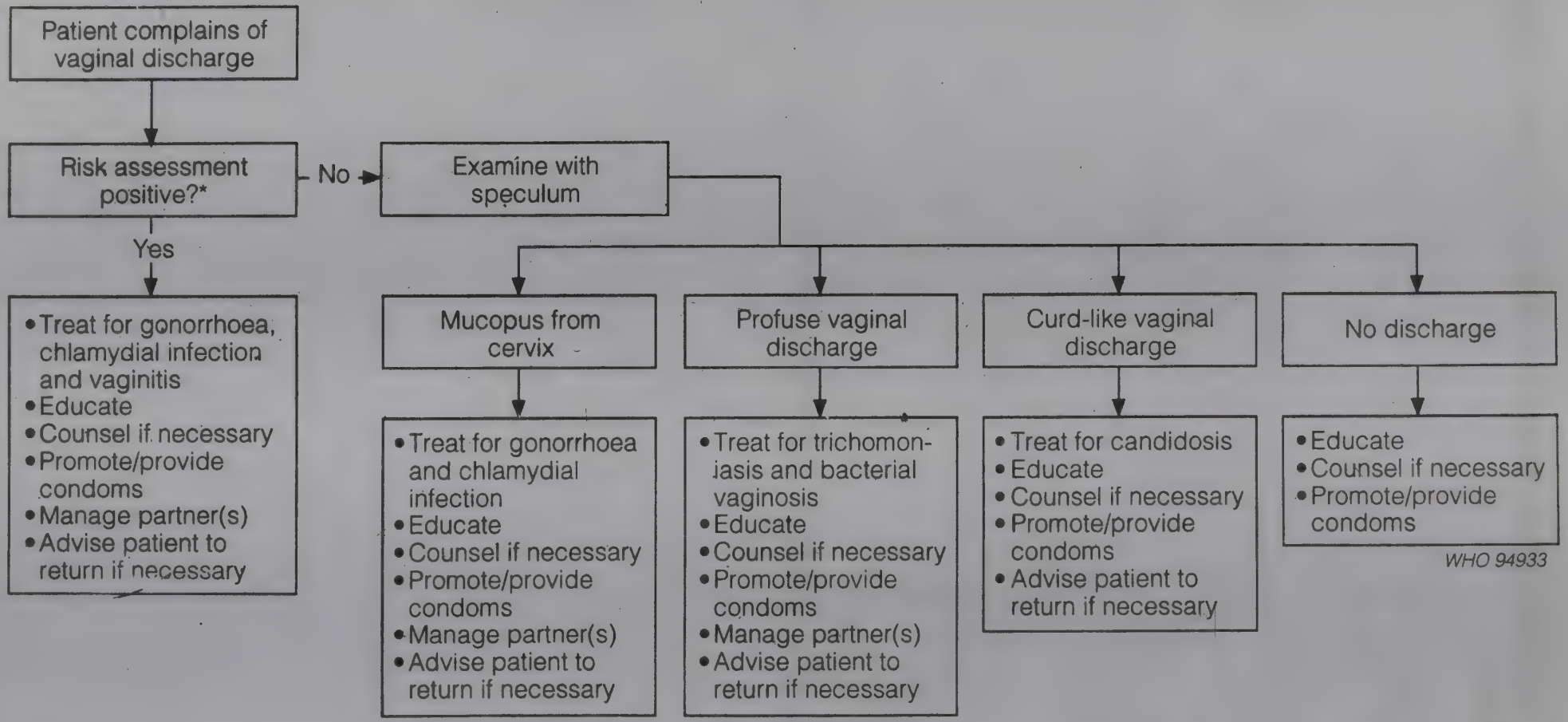


aginal discharge (vaginal examination and laboratory tests ot possible)



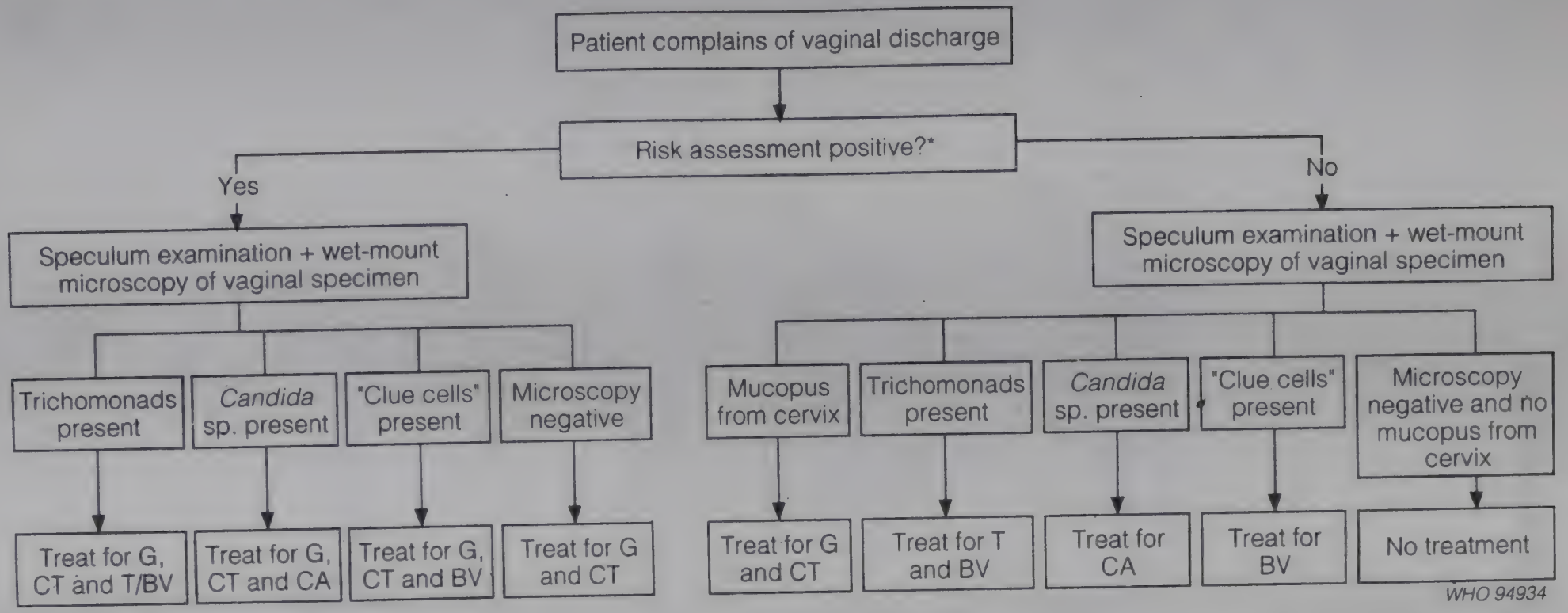
The risk assessment is positive if the patient's partner is symptomatic or if any two of the following apply o the patient: age <21 years; single; >1 partner; new partner in the past 3 months.

Vaginal discharge (speculum available)



* The risk assessment is positive if the patient's partner is symptomatic or if any two of the following apply to the patient: age <21 years; single; >1 partner; new partner in the past 3 months.

Vaginal discharge (speculum and microscope available)



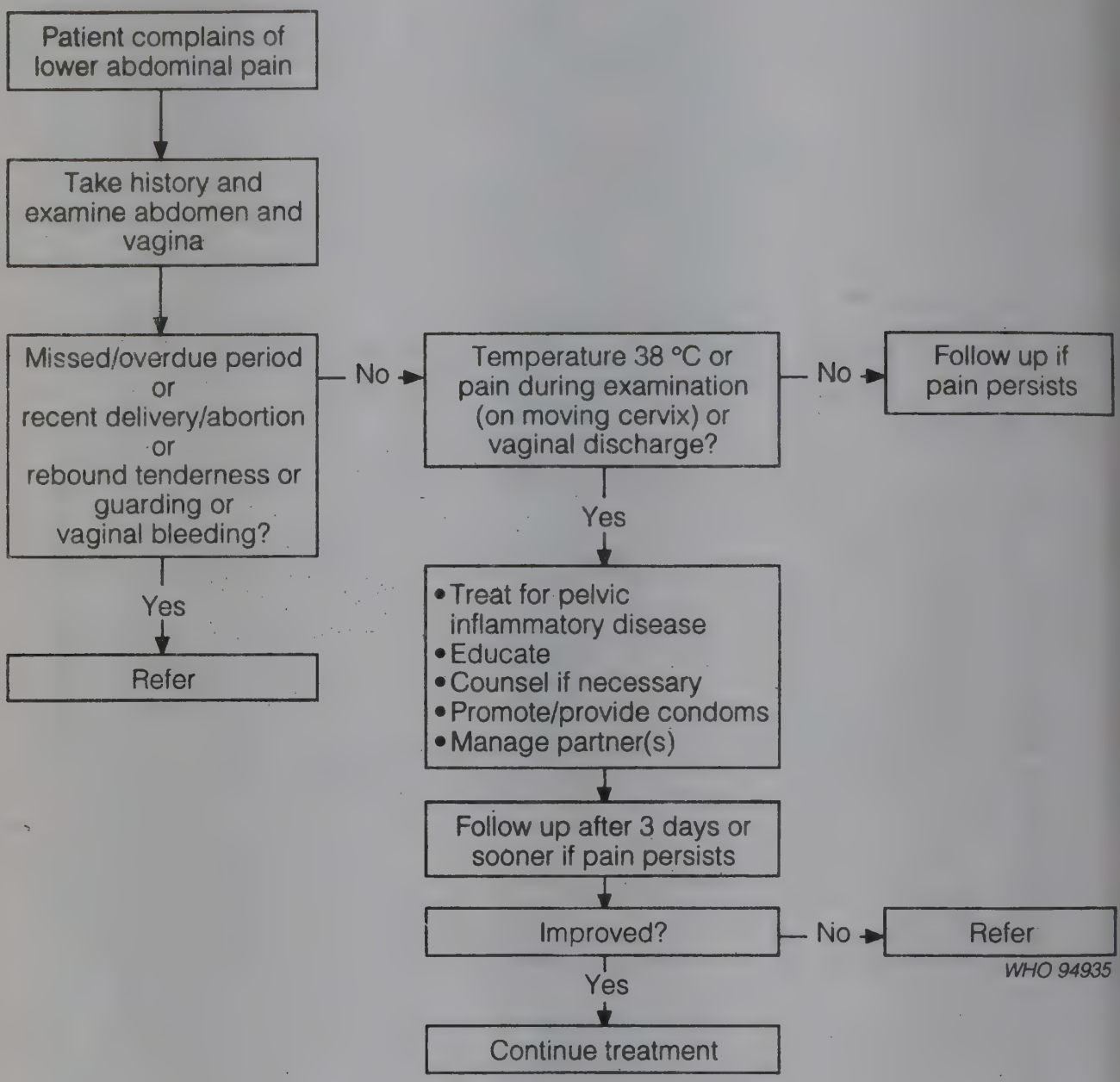
For all patients:

- Educate
- Counsel if necessary
- Promote/provide condoms
- Manage partner(s)
- Advise to return if necessary

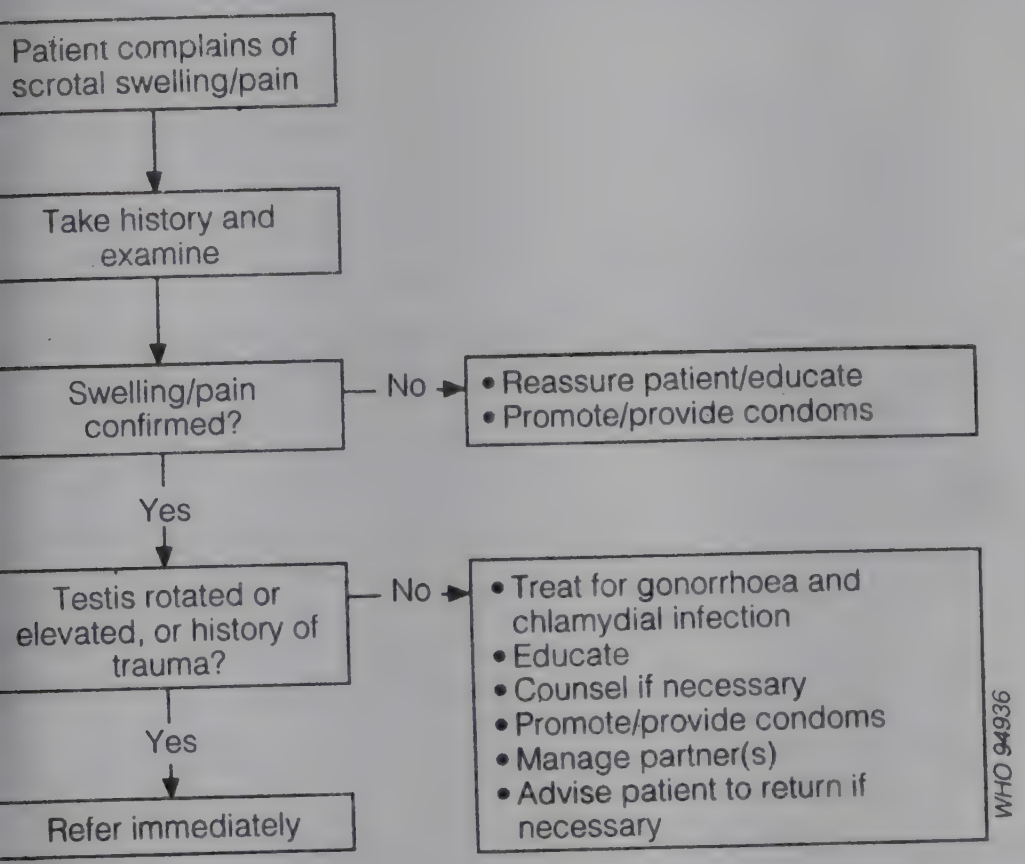
G: Gonorrhoea
CT: Chlamydial infection
T: Trichomoniasis
CA: Candidosis
BV: Bacterial vaginosis

* The risk assessment is positive if the patient's partner is symptomatic or if any two of the following apply to the patient: age <21 years; single; >1 partner; new partner in the past 3 months.

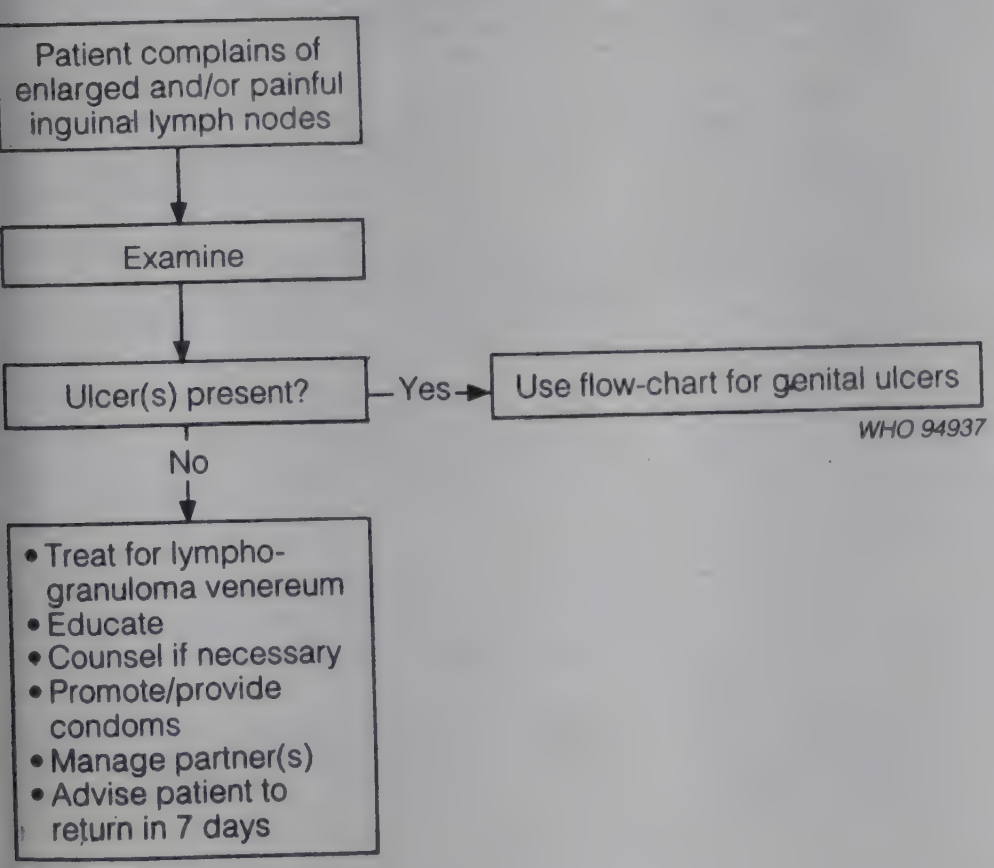
Lower abdominal pain in women



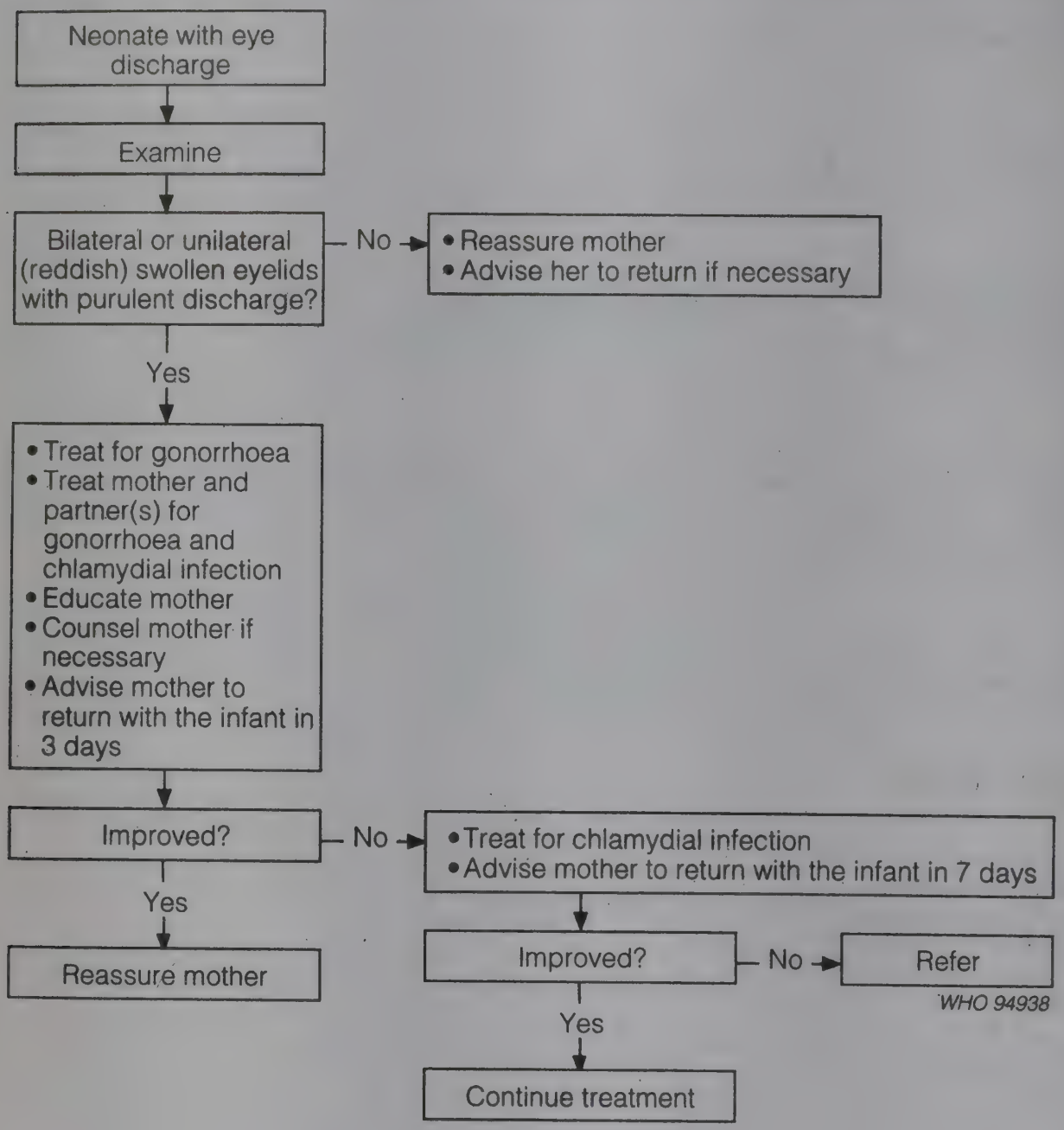
crotal swelling



Inguinal bubo



Neonatal conjunctivitis (laboratory support not available)



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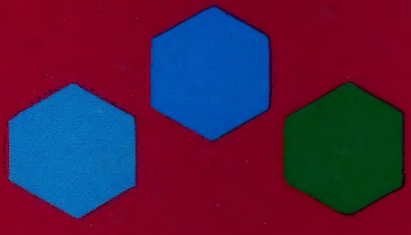

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